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Castor Oil-Based Biodegradable Polyesters

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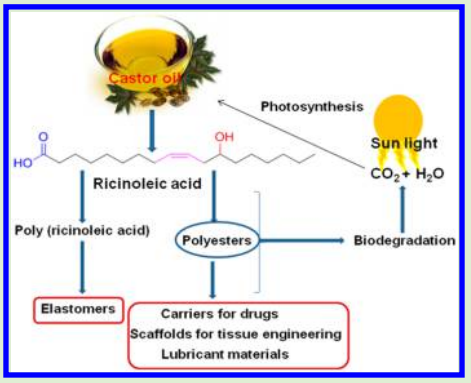
ABSTRACT: This Review compiles the synthesis, physical properties, and biomedical applications for the polyesters based on castor oil and ricinoleic acid. Castor oil has been known for its medicinal value since ancient times. It contains ~90% ricinoleic acid, which enables direct chemical transformation into polyesters without interference of other fatty acids. The presence of ricinoleic acid (hydroxyl containing fatty acid) enables synthesis of various polyester/anhydrides. In addition, castor oil contains a cis-double bond that can be hydrogenated, oxidized, halogenated, and polymerized. Castor oil is obtained pure in large quantities from natural sources; it is safe and biocompatible.



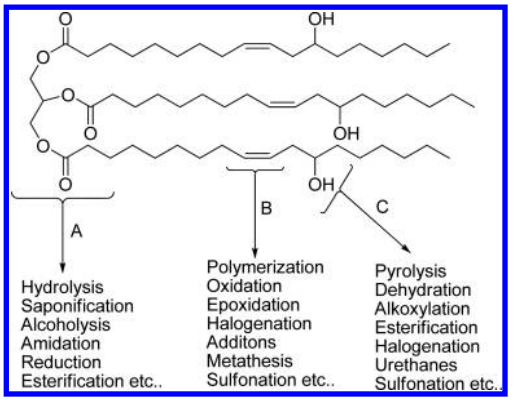
1. INTRODUCTION

Polyesters are the first synthetic condensation polymers prepared by Carothers' during 1930s.[1,2] They are biodegradable and environmentally friendly. The ester linkages hydrolyze and degrade into smaller fragments under physiological conditions. Moreover, they are degraded by micro-organisms such as algae, bacteria, and fungi. Polyesters are not restricted in biomedical applications, but may be extended to the preparation of elastomers, and packaging materials.[3,4]

Vegetable oils are renewable resources with possibilities for chemical modifications. They are inexpensive; the chemical industry considers them as a petroleum alternative. Fatty acids (saturated and unsaturated) from vegetable oils may serve as starting materials for the synthesis of biobased polymers.[5] Most vegetable oils contain fatty acids with chain lengths from 12 to 22 carbon atoms and up to three double bonds. These acids serve as monomers for further polymerization through chemical modifications. Fatty acids are naturally occurring and may be chemically modified to have readily hydrolyzable bonds.[6−9]

Among the vegetable oils, castor oil has been used for preparation of different biodegradable polymers.[10,11] Castor oil (also called *Oleum Palmae Christi*) is obtained from the seeds of the plant *Ricinus communis* and has been known for its medicinal value since ancient days.[12,13] The medicinal value of castor oil was first described in the Ebers papyrus of ancient Egypt 3500 years ago.[14] Castor oil was primarily used as a purgative/laxative to counter constipation. It hastens uterine contraction by activating prostaglandin EP_3 receptors.[15] However, it has a nauseating property, and it is therefore classified as nonedible oil. Castor oil contains about 90% of a hydroxylated unsaturated fatty acid called ricinoleic acid [(9*Z*, 12*R*)-12-hydroxyoctadec-9-enoic acid] (RA). A substantial amount of RA in castor oil makes it unique among other vegetable oils.[16] Scheme 1 describes the possible chemical modifications of different reactive sites of castor oil.[11]

Scheme 1. Possible Chemical Modification Sites[a] and the Reactions for the Preparation of Various Derivatives of Castor Oil[11]



[a](A) Ester modification; (B) double bond modification; (C) hydroxyl group modification.

2. IMPORTANCE OF CASTOR OIL/RICINOLEIC ACID IN THE PREPARATION OF BIODEGRADABLE POLYESTERS

Fatty acids scaffolds are desirable biodegradable polymers, but they are restricted as they are monofunctional (most of the fatty acids have single carboxylic acid group). Ricinoleic acid is one of the few naturally available bifunctional fatty acids with an additional 12-hydroxy group along with the terminal carboxylic acid (Scheme 2). This hydroxyl group provides additional functionality for the preparation of polyesters or

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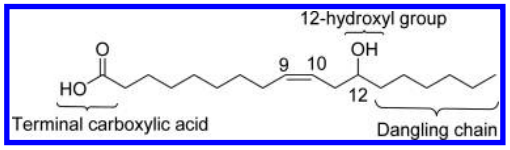
Scheme 2. Structure of Ricinoleic Acid, a Bifunctional Monomer for the Preparation of Biodegradable Polyesters from Castor Oil



polyester-anhydrides. The dangling chains of the ricinoleic acid impart enough hydrophobicity to the resulting polyesters, influencing the mechanical and physical property of polymers. These chains act as plasticizers by reducing the glass transition temperatures of the polyesters.[17]

Polymers with castor oil/ricinoleic acid may be fine-tuned as required for flexibility, hydrophobicity, and injectability.[18] Copolymerized or cross-linked castor oil/ricinoleic acid polymers yield interesting thermo plastic or thermosetting elastomers. These properties lead to further exploration of these materials having an additional biobased character.

3. SYNTHESIS OF CASTOR OIL/RICINOLEIC ACID BASED POLYESTERS

Castor oil or ricinoleic acid based polyesters are synthesized primarily by polycondensation (bulk synthesis) or by ring opening polymerization (ROP), the latter method being more advantageous. ROP generally yields high molecular weight homo or copolymers, with shorter and milder reaction conditions. High conversions can be obtained without the removal of byproducts compared to polycondensation reactions.[19,20] Catalysts used for ROP include: *p*-toluenesulfonic acid, trifluoromethanesulfonic acid (strong acids), metal oxides of antimony trioxide, Lewis acids such as titanium tetrabutoxide, tin acetate, or tin octanoates, and weak acid salts of alkali metals or alkaline earth metals.[21] Enzymatic catalysis have also been reported in the synthesis of castor oil-based polyesters.[22,23] Different polyesters are obtained with different properties depending on the monomers (Table 1 and Table 2).

3.1. Polycondensation Polymerization. Polycondensation is a widely used method to synthesize either homo or copolymer of ricinoleic acid (RA). We review a few examples of polyester synthesis through polycondensation. They generally involve high vacuum and high temperature. The generated water must be removed from the reaction medium time to time to increase the conversion and molecular weight.

RA and lactic (LA) acids copolyester were synthesized by thermal polycondensation (~150 °C). This method resulted in random P(RA-LA) copolyesters (M_w 2000−8000). Polyesters containing >20% RA were liquid at room temperature. Transesterification of high molecular weight poly(lactic acid) (PLA) with RA followed by repolyesterification (at 150 °C for 12 h) resulted in multiblock P(PLA-RA) copolyesters (Scheme 3).[24] The molecular weights of these polyesters were in the range of 6000 and 14000 Da. Polymers containing 50% RA were viscous liquid at room temperature. Polymer structures were confirmed by ^{1}H NMR spectroscopy and with DSC. Polymers prepared by thermal polycondensation were random copolymers ($h > 1$), whereas copolymers prepared by transesterification have a multiblock in nature ($h < 1$). DSC analysis revealed crystalline structure for the polyester synthesized by transesterification. Polyesters synthesized by random condensation, polymers of P(LA-RA) 90:10 w/w contained crystalline domains. The liquid polyesters may be used as sealants and as injectable carriers of drugs.[24]

Slivniak et al. synthesized and studied the stereocomplexation of LA and RA copolyesters. Copolyesters P(LA-RA)s were synthesized by both polycondensation and transesterification using different PLA blocks (Scheme 4). ^{1}H NMR and DSC studies revealed correlation between the degree of crystallinity and PLA block size. Polymer P(L-LA-RA)s and its enantiomer D-PLA were mixed to form stereocomplex in acetonitrile. Minimum 10 lactic acid units are required to form a stereocomplex from P(L-LA-RA)s. The resulting stereocomplexes exhibited higher melting temperature than the corresponding enantiomerically pure polymers. These stereocomplexes have been used as a drug carriers and scaffolds for tissue engineering. These copolyesters are low-melting biodegradable polymers with desirable properties such as pliability, hydrophobicity, and softness.[25]

In another study, Slivianic et al. reported the degradation and drug release from L-LA and RA copolyesters. Three types of polymerization methods were used: (a) ROP, (b) melt condensation, and (c) transesterification. They obtained molecular weights between 3000 and 13 000 Da. The polymers showed zero-order weight loss kinetics (~20−40% loss after 60 days of incubation). Weight loss is proportional to the lactic acid release. M_w sharply decreased during the first 20 days followed by steady slow degradation (M_n ~ 4000−2000 Da) for another 40 days. The synthesized P(LA-RA) 60:40 w/w is hydrophobic and amorphous, but L-PLA is crystalline. Increased hydrophobicity accounts for a similar degradation rate.[26]

Hyperbranched polymers were prepared by condensation polymerization. AB_x types of monomers are attached to a core molecule, and polymerization is usually carried out in the presence of catalysts. The synthesized hyperbranched polymers can be purified by less expensive methods with higher yields.[27,28] A novel type of hyper branched resin (HBR) was synthesized using dipentaerythritol, dimethylolpropionic acid, and RA. The reaction was carried out using *p*-TSA acid (0.4%w/w) at 140 °C for 3−4 h in the first step, followed by adding stiochiometric ratios of dimethylolpropionic acid. Castor oil fatty acids were then added in the next stage, and the reaction was conducted at 220 °C (Scheme 5). The molecular weight (M_w) of HBR was ~23100 Da; the average molecular weight (M_n) was determined to be ~10 900 Da. Unreacted hydroxyl groups of RA in HBR polymer make hydrogen bonds with drug molecules, a choice polymer for controlled drug delivery.[29]

Castor oil-based polyester was synthesized by simple, catalyst-free melt condensation using the following biocompatible monomers: mannitol, sebacic acid, and citric acid (Scheme 6). These polymers have desirable mechanical, hydration, and biocompatible properties. The polymers degrade completely in ~21 days.[30]

A series of polyesters were synthesized by melt condensation with sebacic acid and the following: citric acid, mannitol, and RA (Scheme 7). Different precursor combinations resulted in a range of elastic modulus (22−327 MPa) and tensile strength (0.7−12.7 MPa). The polymers showed rubber-like behavior at body temperature (37 °C). Contact angles were in the range of 42° to 71°, making them ideal for drug delivery. Contact angles for the tough cured polymers are higher, compared to mild cured counterparts. Curing makes the polymer more hydrophobic. Contact angles increase with content of citric acid due to the cross-linking. If citric acid did not participate in cross-linking, the unreacted citric acid would have caused a decrease

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Table 1. Summarized Literature on the Ricinoleic Acid-Based Polyesters

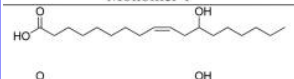
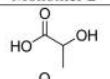
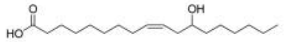
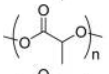
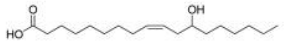
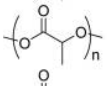
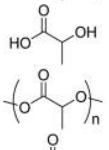
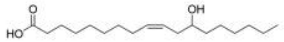
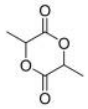
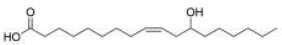
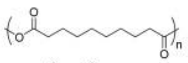
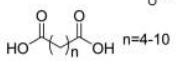
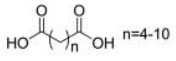
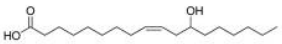
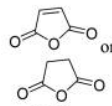
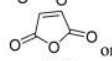
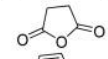
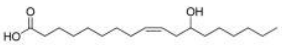
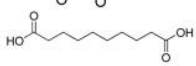
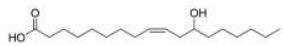
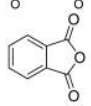
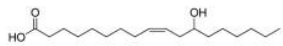
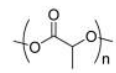
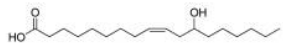
Monomer 1	Monomer 2	M_w [Da]	Comments/note	Ref.
		2000 - 8000	Copolyesters by polycondensation. T_m 55-98 °C	24
		6000 - 14000	Copolyesters by transesterification and repolymerization. T_m 93-147 °C.	24
		3000 - 5000	Stereocomplexes of ricinoleic acid and polylactic acid	25
		3000-13000	Copolyesters prepared using ROP, random condensation, transesterification. Their hydrolytic degradation and drug release capacities were studied.	26
	Dipentaerythritol and dimethylol propionic acid.	≈23100	Hyperbranched resin prepared	27
	Sebacic acid, citric acid and D-mannitol	-	The synthesized polyesters are used as tissue engineering scaffolds, and also for localized drug delivery.	29
	1,3-propane diol and 	M_n 13000-61000	Triblock copolyesters were prepared by AB type self condensation followed by ROP.	31
		2000 - 60000	Poly(ester anhydride)s prepared by transesterification. T_m 24-77 °C	32
Oligoricinoleic acid (Mn ≈1200)		5500 - 8300	Pasty injectable polymers except poly(SARA). T_m 31-47 °C	33
Polyricinoleic acid (Mn ≈3000)		9200 - 13000	Non-injectable poly(ester-anhydrie)s. T_m 60-63 °C	33
		4000 - 4900	Injectable pasty poly(ester-anhydride)s. T_m<30 °C.	33
Oligoricinoleic acid (Mn ≈1200)		4400- 5500	Injectable pasty poly(ester-anhydride)s. T_m ≈30 °C.	33
Polyricinoleic acid (Mn ≈3000)		4400 -5500	Very viscous, difficult to injectable poly(ester-anhydride)s. T_m 50-51 °C.	33
		12000	Poly(ester-anhydride)s for antimicrobial coatings were prepared. T_m 112 °C.	34
		5100	Poly(ester-anhydride)s studied for its usage for the releasing of antimicrobial agent diuron.	34
Ricinoleic acid comonomer	Bile acid based monomer	140000- 28000	Copolyesters were prepared by entropy driven RO metathesis polymerization. T_g -60 to 11.2 °C.	35
		-	5%wt. of castor oil incorporation into poly(L-lactic acid) was increased with its tensile toughness 7 times greater than poly(L-lactic acid).	36
	Polyesters of adipic/sebacic acid with 1,4-butane diol/1,3-propyleneglycol/ ethylene glycol	3000-6600	High M_w polyesters were prepared using inorganic acid as catalyst.	37

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Table 1. continued

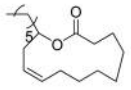
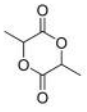
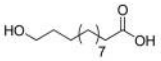
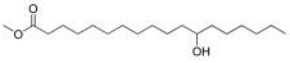
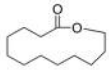
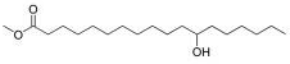
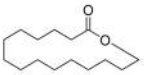
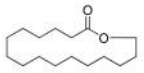
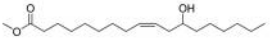
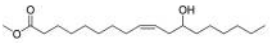
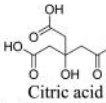
Monomer 1	Monomer 2	M_w [Da]	Comments/note	Ref.
	Diethylene glycol, trimethylol propane or pentaerythritol	1130-8300	Polyesters prepared were crosslinked with trimethylolpropanetriacrylate.	39
	-	-	A nanocomposite using iron oxide nanoparticles dispersed in RA polyester matrix and behaves as a supermagnetic material.	40
	Poly(butylenes succinate) vinyl imidazolium salt	-	Antimicrobial copolyesters	41
		5000-16000	RA lactones copolymerize with lactide (LA) through ROP using Sn(Oct) as a catalyst. T_m 105-189 °C	43
	-	100600	Polyricinoleate using lipase catalysis and was cross-linked with dicumyl peroxide. T_g -74.8 °C	44
		≈100000	Copolyesters using lipase catalysis. T_m -56 to 85 °C. Young's modulus decreased with 12-hydroxy methyl strearate (12-HSM).	45
		149000-237000	Copolyesters using lipase catalysis. T_m 8.74-87.4 °C, Young's modulus 1.5-115 MPa.	49
		234000-290000	Copolyesters using lipase catalysis. T_m 42.9-96.5 °C, Young's modulus 3.46-123 MPa.	49
		172000- 91000	Copolyesters using lipase catalysis. T_m 44.9-96.5°C, Young's modulus 6.86-206 MPa.	49
	Dimerdiol, trimethylolpropane pentaerythritol	724- 4850	Star polymers by lipase catalysis. T_m -7.5 to -18.9 °C	50
	-	272000	Epoxy ricinoleate and polyepoxyricinoleate were prepared using lipase and crosslinked with maleic anhydride to produce chloroform insoluble film.	51
	-	100800	A smooth and nonsticky surface elastomer prepared by lipase catalyzed polymerization and subsequent vulcanization of methyl ricinoleate via polyricinoleate.	52

Table 2. Summarized Literature on Castor Oil-Based Biodegradable Polyesters

Monomer 1	Monomer 2	M_w [Da]	Comments/note	Ref.
Castor oil	Sebacic acid, citric acid, mannitol	8223	Copolyesters for drug delivery	28
Castor oil		3000-5700	Star shaped polyester polyols based on castor oil and L-lactide were prepared using trifluromethanesulfonic acid as a catalyst.	30
Castor oil	Polyesters of adipic/sebacic acid with 1,4-butane diol/1,3-propyleneglycol/ ethylene glycol	3000-6600	High M_w polyesters were prepared using inorganic acid as a catalyst.	37
Maleic acid-castor oil monoester	Styrene	M_n 44100	Copolyester with styrene has excellent thermal stability and biodegradability.	38
Castor oil	 Citric acid	11000 M_n 7000	Branched copolyesters of castor oil and citric acid were synthesized. These polymers are viscous, injectable, and may be used as soft tissue augmentation.	42, 45
Castor oil-based hyperbranched polyester polyol (HBPP) of monoglyceride of oil	bis(hydroxymethyl)propionic acid	-	Hyper branched epoxy was prepared as a biodegradable material.	43
Castor oil	Succinic acid	>8000, degree of polymerization 8.	Castor-succinate polyesters prepared and functionalized for the application in personal care materials.	47
Castor oil	Pentaerythritol, maleic anhydride	-	Prepared biobased unsaturated polyester resin containing highly functionalized castor oil.	48

in the contact angles. Also, increase in sebacic acid and RA content increases the contact angles.The polymers erode from the surface or inside out (bulk), depending on how it is cured. These polyesters exhibit significant attachment to smooth muscle cells (C2C12 myoblast cells, oriented growth in3 days). Therefore, they are potential tissue engineering scaffolds.[31]

There are biodegradable-branched polyesterpolyols based on L-lactide and castor oil prepared using trifluoromethanesulfonic acid as a catalyst. The polyester polyol was synthesized by the

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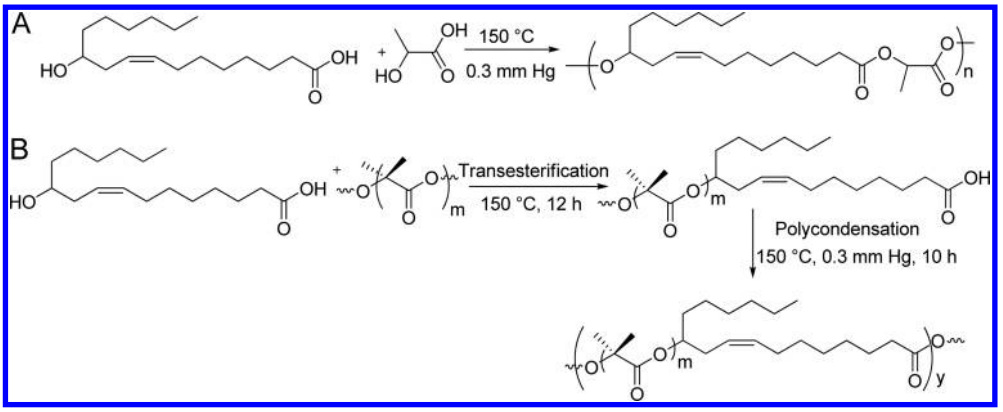
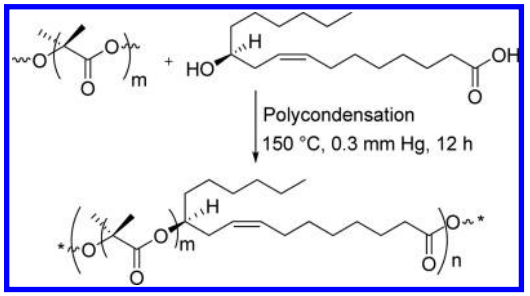
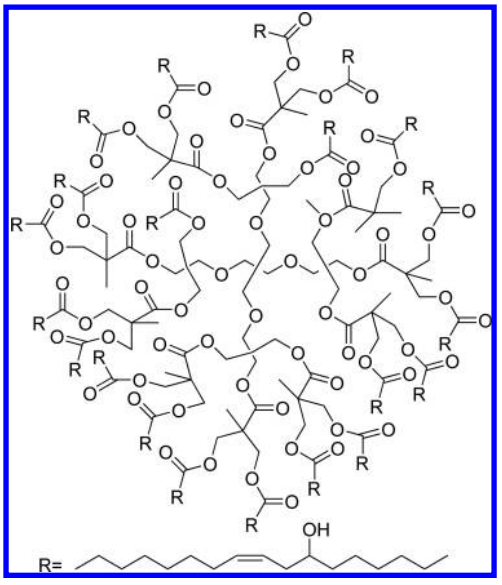
Scheme 3. (A) Synthesis of Poly(RA-LA) Condensation Polymers and (B) Synthesis of Poly(RA-LA) by Transesterification of Polylactic Acid and RA Followed by Repolyesterification[24]



Scheme 4. Synthesis of P(LA-RA)s 80:20 with Different PLA Chain Lengths (m = 2−20)[25]



Scheme 5. Synthesis of Ricinoleic Acid Based Hyperbranched Polymers for Controlled Drug Delivery[29]

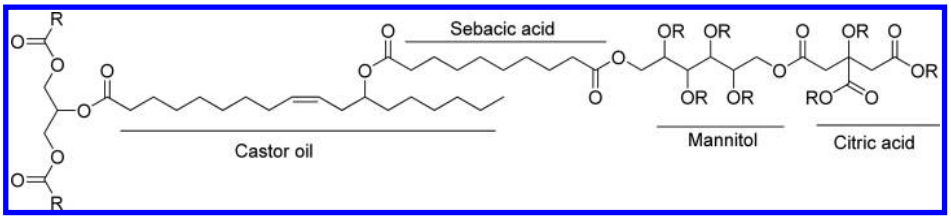


"core-first" method, involving polymerization of L-lactide by using a castor oil as a multifunctional initiator (Scheme 8). FTIR and ^{1}H NMR spectroscopy confirmed the polyesters. The band for carbonyl (C═O) of aliphatic ester splits into two bands, one at 1758 cm^{-1} for poly(L-lactide) chains, and the other one at 1745 cm^{-1} for castor oil from the FTIR spectrum. A band for ═C−H stretching of RA from castor oil appeared at 3009 cm^{-1} in polyester polyol, as well as bands from asymmetric (2945 cm^{-1}) and symmetric (2855 cm^{-1}) −CH_2 vibrations with an additional weak shoulder around 2997 cm^{-1} from − CH_3 of terminal methyl group in fatty acid of castor oil. Strong absorption at 3500 cm^{-1} originated from terminated hydroxyl groups, −OH at poly(L-lactide) chains. In the ^{1}H NMR spectrum for the lactide polymerization with castor oil hydroxyl groups, the peak related to C12 proton attached to the hydroxyl group (CH−OH) at 3.61 ppm disappeared, while a new peak at 4.32 ppm appeared. This confirms the hydroxyl is connected to lactide chains. M_w of these polyester polyols is between 3000 and 5700 Da.

The authors reported polymer branching influence thermal properties like melting, glass transition temperature, and degree of crystallization. Longer chain branches enhance crystallization; short-chain branches inhibit them. They observed castor oil content affected the stereoregularity of polymers, consequently altering their thermal properties. Cationic polymerization with trifluoromethanesulfonic acid provided regular polymer structure. The crystallization and melting is influenced by arms length. Most of their synthesized polymers are primarily crystalline (degree of crystallinity >50%).

Thermal stability studies show dependence of weight loss on arm length for the star-shaped polyesters during heating process. The polymers primarily degrade through transesterification. TGA curves show degradation at temperature >300 °C. Polymers with the same arm number revealed that weight loss becomes less with increasing the arm length-longer arms depict higher molar mass. They proposed a cyclization mechanism

Scheme 6. Castor Oil-Based Polyesters Prepared from Sebacic Acid, Mannitol, and Citric Acid[30]



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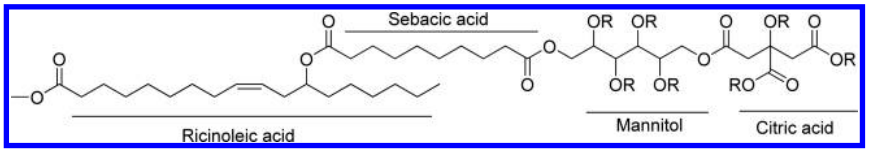
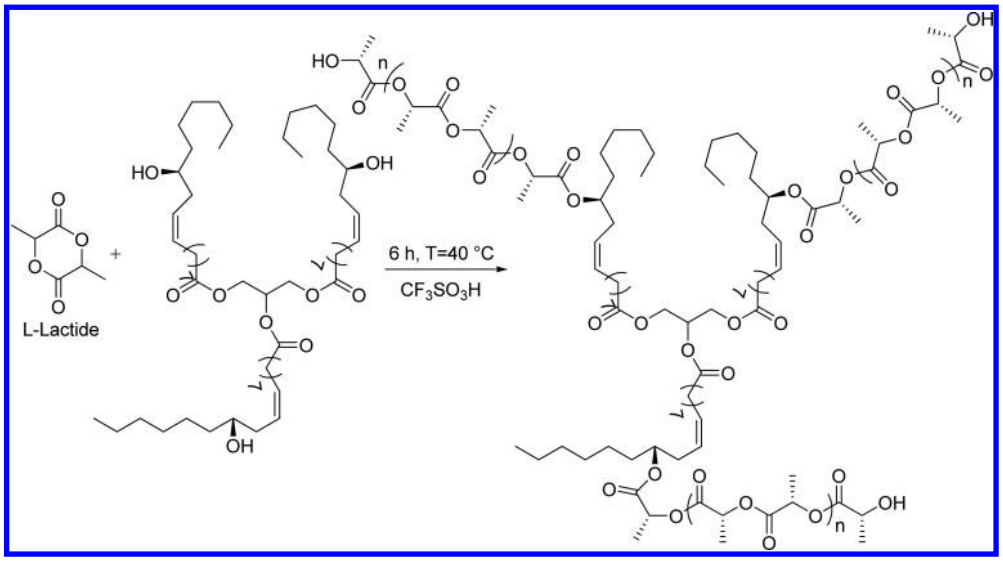
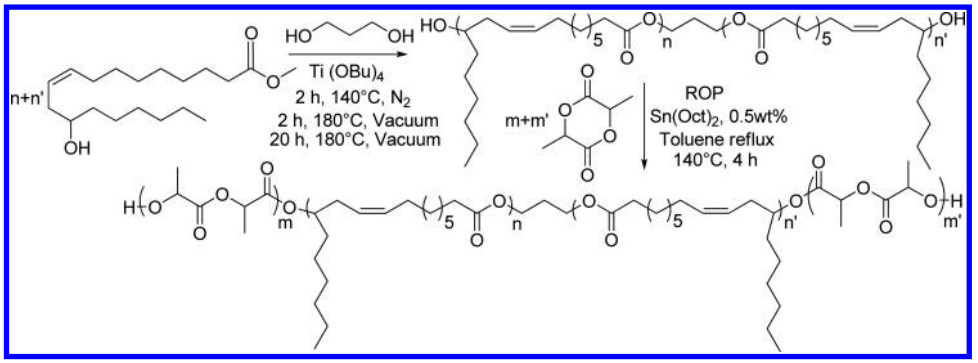
Scheme 7. New Class of Ricinoleic Acid Based Polyester Prepared with Sebacic Acid, Citric Acid, Mannitol, and RA[31]



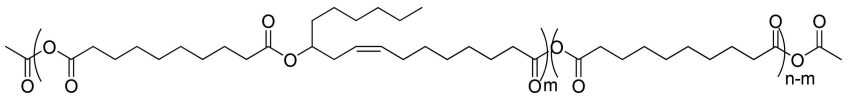
Scheme 8. Synthesis of Star-Shaped Polyester Polyol by a Cationic Mechanism[32]



Scheme 9. Two-Step Procedure to PLLA-*b*-PRic-*b*-PLLA Triblock Copolymers[33]



Scheme 10. Chemical Structure of Poly(PSA-RA) Prepared from Polysebacic Acid and RA[35]



(impossible in linear poly lactides) between terminal −OH and $-C(O)OSO_2CF_3$ end-groups. These groups allow end-to-end cyclization. The cyclic nature of the resulting polymer explains its higher thermal stability as compared with linear poly(L-lactide). The polymers are generally low melting.[32]

Lebarbe et al. synthesized ABA -type triblock poly(L-lactide)-*b*-poly(ricinoleic acid)-*b*-poly(L-lactide) aliphatic copolyesters (Scheme 9). Methyl ricinoleate was condensed to a small amount of 1,3-propanediol to prepare *α,ω*-hydroxy-terminated poly(ricinoleic acid) with a molar mass of 11000 g/mol. L-lactide polymerization was initiated from terminal hydroxyl moieties of *α,ω*-hydroxy-terminated poly(ricinoleic acid). This strategy led to triblock copolymers, with composition ranging from 35 to 83 wt % of poly(lactic acid). They displayed multistep thermal degradation, 5% weight loss in the range 175−225 °C. DSC reveals polyRA block has a moderate effect on PLLA melting behavior.[33]

Soybean and castor oil-based monomers were functionalized with maleic anhydride followed by alcoholysis of the oils with various polyols, such as pentaerythritol, glycerol, and bisphenol A propoxylate. The styrene copolymers are hard rigid plastics, but the castor oil based copolymers were significantly plasticity. On the other hand, the strength, and T_g (9 °C higher) values were higher compared to soybean-oil-based polymers.[34]The castor oil-based polymers are more cross-linked compared to the soybean oil based polymers, due to the functionalized fatty acid chains.

Poly(ester-anhydride)s were prepared by the melt polycondensation of diacid oligomers of poly(sebacic acid) (PSA), transesterified with RA (Scheme 10). PSA with RA are reacted

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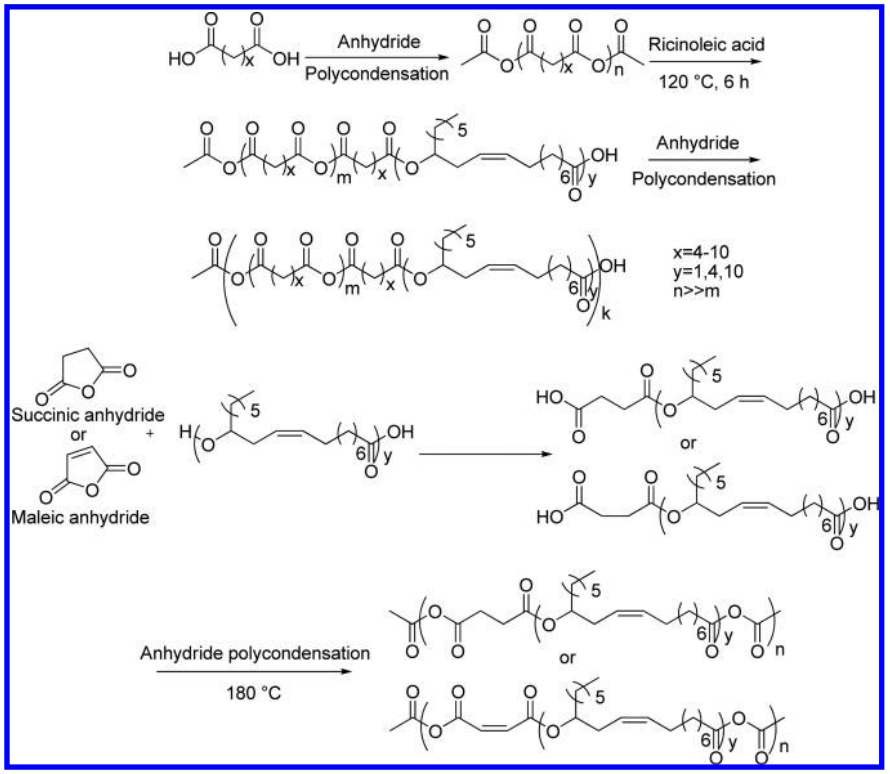
Scheme 11. Synthesis of Poly(ester-anhydride)s of RA and Alkanedioic Acids, Maleic and Succinic Anhydrides[36]



to form oligomers followed by polycondensation to form random copolymers of SA-RA. M_w vary from 2000−60000 Da and T_m of 24−77 °C, with PSA containing 20−90% (w/w) RA. These new biodegradable copolymers have been used as drug carriers.[35]

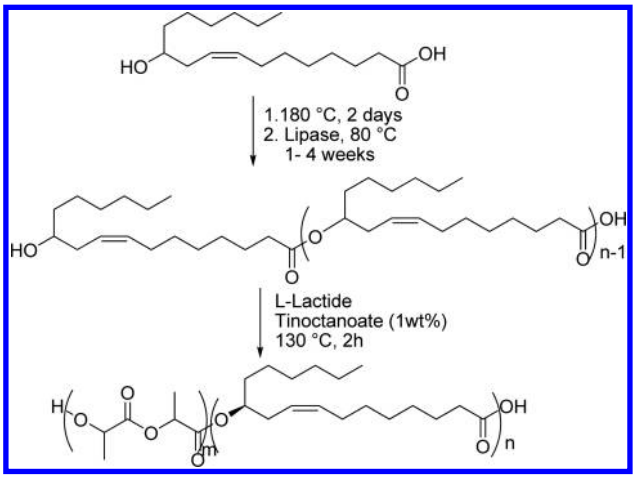
Our group synthesized injectable poly(ester-anhydride)s from RA and its oligoesters by transesterification and repolymerization (Scheme 11). A decrease in melting points was observed with the length of alkane dicarboxylicacid from C12 to C6 of poly(ester-anhydride)s. Poly(ester-anhydride)s prepared with dodecandioic, sebacic, suberic, adipic, and ricinoleic acids were in injectable nature. Poly(ester-anhydride)s prepared using RA oligomers produced higher melting polymers. Copolymers of RA with maleic or succinic anhydrides were also pasty and injectable. These polymers were degraded to their fatty acids counterparts. They have been used for controlled drug delivery.[36]

Poly(ester-anhydride) with antimicrobial protection coatings composed of RA, sebacic acid, terephthalic acid, and isophthalic acid was reported. Hydrolysis and controlled release were studied in the buffer phosphate and in water with different analytical methods. The mixture of the polymer with various fillers proved that poly(ester-anhydride)s are compatible with paint preparation. The in vitro experiments showed that for months the polymers could release diuron (an antimicrobial agent). The results of the study demonstrate that these copolymers can be applied to potential environmental applications in the medical field.[37]

Copolyesters based on bile acid and RA were synthesized via entropy-driven ring-opening metathesis polymerizations. They displayed tunable mechanical properties and heterogeneous degradation behavior. The T_g and Young's modulus may be adjusted by varying the comonomers. They may find a widerange of applications, such as tissue regeneration and drug delivery.[38]

Adding 5 wt % castor oil to PLLA significantly enhances tensile toughness. The polymerization was carried out through enzyme (lipase) catalyzed condensation. The resulting RA

Scheme 12. Synthesis of Polyricinoleic Acid and Poly(ricinoleic acid-L-lactic acid)[39]



polymers containing hydroxyl end groups that were subsequently used to initiate the ring-opening polymerization of L-lactide (Scheme 12). PLLA-castor oil blend exhibited a tensile toughness 7 times greater than neat PLLA.[39]

Polyesters of adipic or sebacic acid and alkanediols were synthesized; the reactions were catalyzed by inorganic acids. Molecular weights of 23 000 Da were obtained for adipic acid and 85 000 Da for sebacic acid−based polyester. The melting point of these polymers was found to be 52−65 °C, and the melt viscosity was 5600−19400 cP. The work describes an alternative method to produce aliphatic polyesters, for possible use as degradable disposable medical supplies.[40]

The maleic acid-castor oil monoester (MACO) was used as a monomer to synthesize a new environmentally friendly copolymer of styrene and MACO (poly-St/MACO), by suspension

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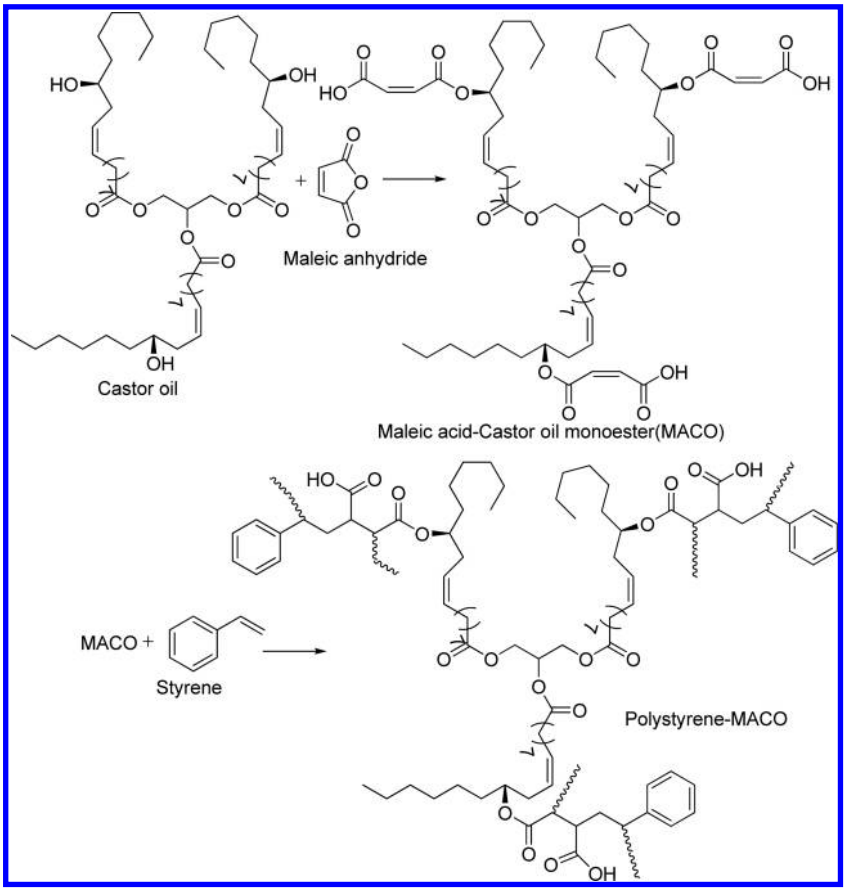
Scheme 13. Synthesis of Maleic Acid-Castor Oil Monoester (MACO) and Polystyrene-MACO[41]



polymerization (Scheme 13). The copolymer yield was 81%, M_w 44100 Da. Poly-St/MACO showed desired biodegradability and potential use as an environmentally friendly material with excellent thermal stability.[41]

Linear and branched polyesters were prepared by transesterification of methyl recinoleate, using diethylene glycol, trimethylolpropane, or pentaerithirtol for different durations. Cross-linked polyesters were prepared by reacting with trimethylolpropanetriacrylate in the presence of benzoylperoxide. These hydrophobic organogels swell in toluene; their cross-linked networks absorb hydrophobic solvents and/or petroleum and other crude oils.[42]

Biopolyesters were prepared using RA and nanocomposites using iron oxide nanoparticles dispersed in ricinoleic acid polyester matrix. A thermogravimetric and magnetic study of this nanocomposite gives good thermal stability and behaves as a supermagnetic material.[43]

Castor oil-derived polyesters with antibacterial activity have been reported (Scheme 14). Unsaturated homopolymer derived from the self-polycondensation of RA and its copolymers with poly(butylene succinate) were synthesized. This copolymer resulted in significant biocidal activity against *Staphilococcus aureus* and a medium efficiency against *Escherichia coli*. Further, the double bonds in the polymer were covalently linked to an antimicrobial molecule (a vinyl imidazolium salt) that significantly enhanced the biocidal activity. This work proposes a general method to link molecules to polyRA units, enabling insertion of new functionalities to the castor oil-derived polyester.[44]

Citric acid−castor oil-based polymers have also been reported: (a) branched viscous polyester (monomer ratio of 93.5:6.5 w/w of castor oil and citric acid) molecular weight of 11000 Da, and (b) cross-linked semisolid polymer (monomer ratio of 92.5:7.5 w/w of castor oil and citric acid). The first polymer (branched) lost less than 10% of its weight during a 30-day degradation study. The synthesized polymers degrade into natural components that were metabolized and eliminated.[45]

Hyperbranched polyester polyol (HBPP) was prepared from monoglyceride of castor oil and bis(hydroxy methyl)propionic acid by polycondensation reaction and in situ generated diglycidal ether of bisphenol A. The structure of HBPP and hyper-branched epoxy was confirmed from FTIR, NMR, and other analytical methods. The poly(amido amine)-cured hyperbranched epoxy exhibited the following mechanical properties: high tensile strength (42 MPa), extensibility (88% elongation), scratch hardness (>10.0 kg), impact resistance (>100 cm), flexibility (bent up to 180° without damage), and biodegradation. Polyol and bisphenol A strongly influence the performance of thermosets. This hyperbranched epoxy can be used as sustainable material as it is a tough, highly elastic, biodegradable and thermostable material.[46]

Castor-succinate polyester is prepared from the castor oil and succinic acid, which is the backbone for a number of functional polymers (Scheme 15). The ratio between castor oil and succinic acid influences the degree of polymerization. If the succinic acid amount increases relative to castor oil, the degree of polymerization will increase, and the polyester will be of lesser polar polyester. Functionalization of this polyester will have applications in the cosmetic formulations.[47]

Castor oil pentaerythritol glyceride maleates (COPERMA) were prepared and used to fabricate a partial biobased

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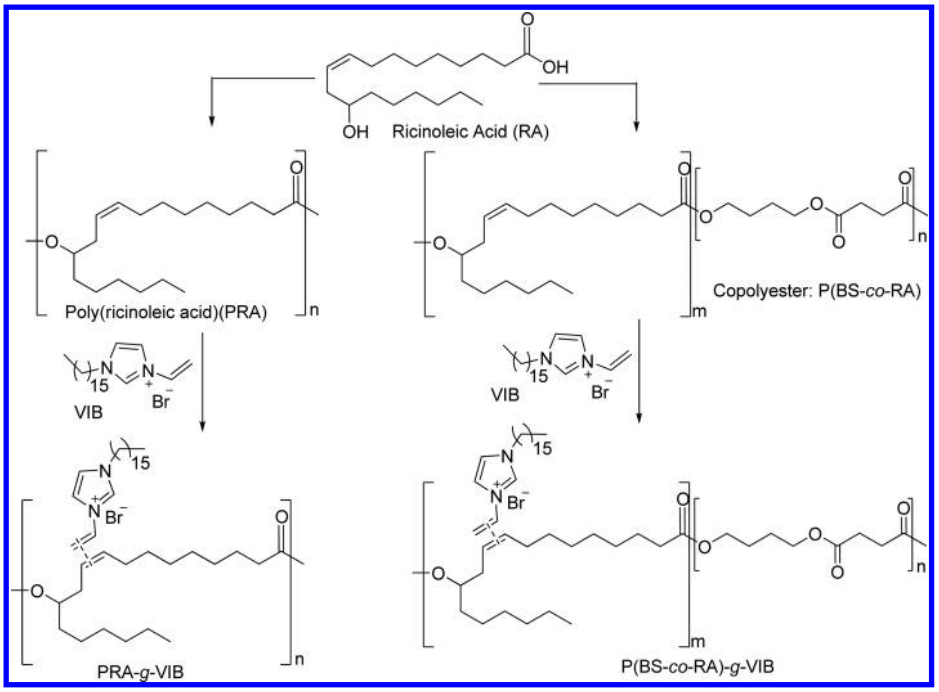
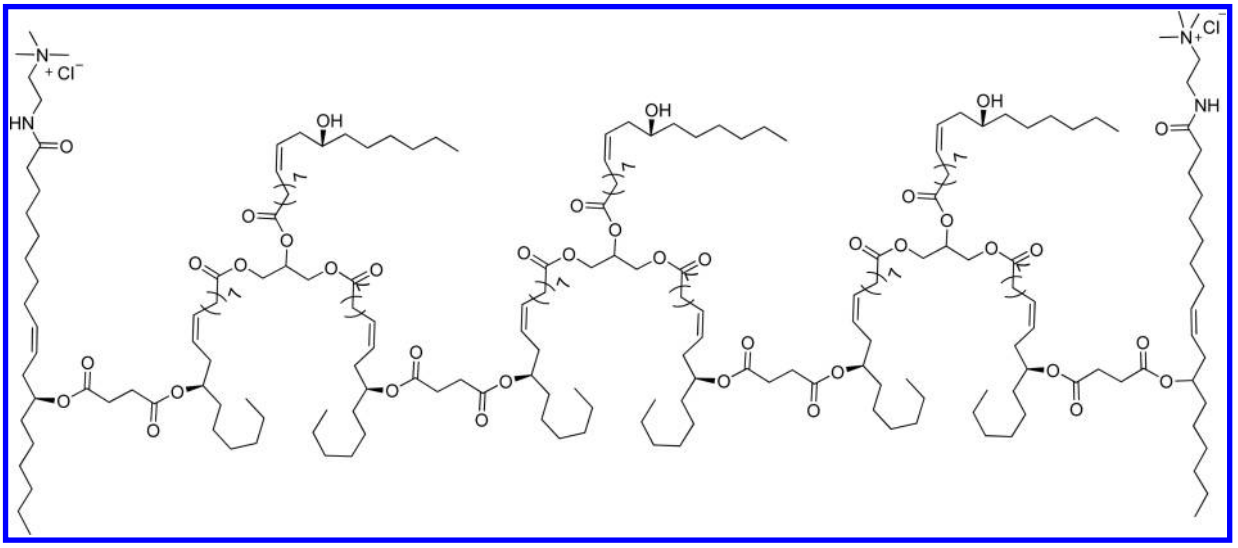
Scheme 14. Polymerization of Poly(ricinoleic acid) (PRA), Polymerization of Poly(butylene succinate-*co*-ricinoleic acid) (P(BS-*co*-RA)), and 3-Hexadecyl-1-vinylimidazolium Bromide (VIB)[47]



Scheme 15. Functionalization of Castor Oil−Succinate Polyester for Personal Care Applications[47]



unsaturated polyester resin (UPR). This COPERMA product was blended with 35 wt % styrene, to prepare a new partial biobased UPR. Physical properties indicate that the resultant biobased resins are suitable for a liquid molding process; they showed less shrinkage than the neat UPR. When the content of COPERMA resin was increased to 20 wt %, tensile strength and storage modulus at 35 °C decreased gradually, but it was greater than reported for other oil/UPR systems. Other properties such as cross-link density, glass transition temperature, tensile and flexural moduli, and impact strength is improved.[48]

3.2. Ring-Opening Polymerization. The major setbacks of polycondensation are the requirement of high temperatures and long reaction periods. Any deviation from the stoichiometry during the reaction resulted in low molecular weight products. ROP is free of all these limitations for the synthesis of polyesters from lactides and lactones. Usually high molecular weight polymers are obtained under mild reaction conditions.[19,20]

Slivniak and Domb synthesized RA lactones, by activation with dicyclohexylcarbodimide and (dimethylamino)pyridine as a catalyst. The lactone was obtained as ∼75% yield. IR and ^{1}HNMR spectra revealed the following: C12 hydroxyl converted to ester, resulted in a shift of C12 proton NMR signal from 3.6 to 2.7 ppm. In FTIR spectrum the −OH broad peak at 3400 cm^{-1}disappeared, and an ester carbonyl peak appeared at 1730 cm^{-1} instead of the carboxylic acid peak at 1700 cm^{-1}. The structures of the macrolactones are given in Scheme 16. Polymerization of the RA lactones by ROP of lactones resulted in oligomers (Table 3). Polymerization with tinoctoate was unsuccessful and yttrium isopropoxide resulted in oligomers. Copolymerization with lactide (LA) by ROP,

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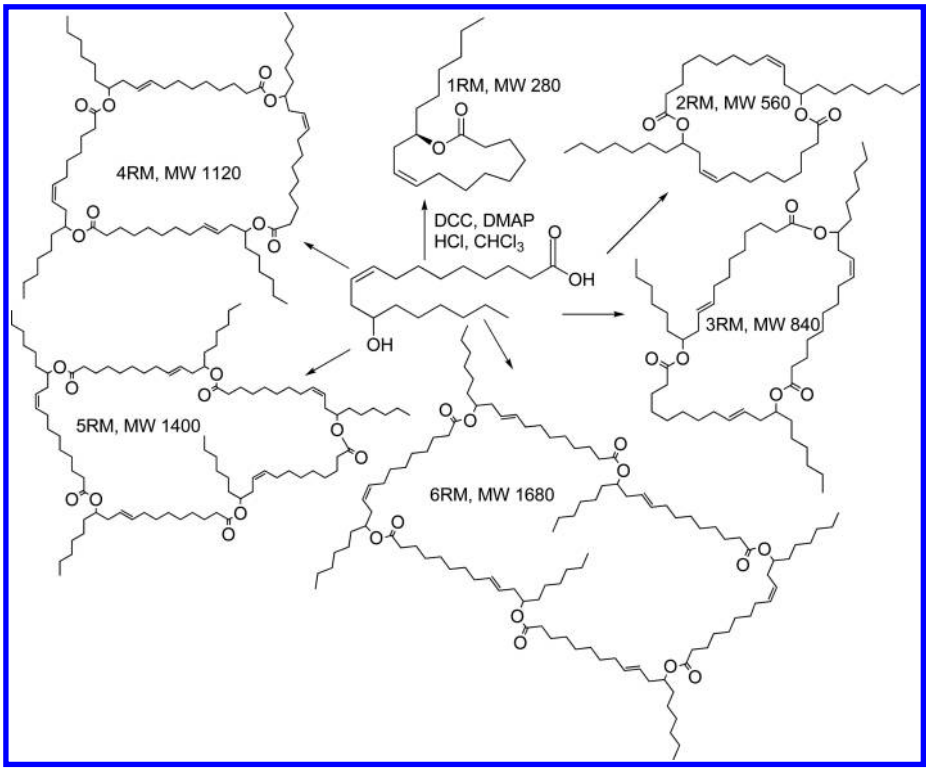
Scheme 16. Showing the Macrolactone Structures Synthesized from RA[a]



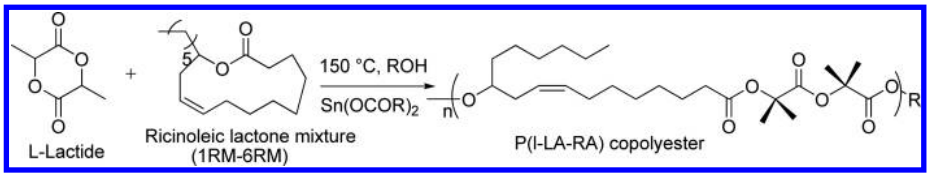
[a]Abbreviations for cyclic macrolactones: **1RM**, monolactone; **2RM**, dilactone, **3RM**, trilactone; **4RM**, tetralactone; **5RM**, pentalactone; **6RM**, hexalactone(All double bonds are with "cis" configuration).[49].

Table 3. Ring-Opening Homopolymerization of a Ricinoleic Lactone Mixture and Pure Monolactone, 1RM, and Dilactone, 2RM (Reproduced with permission from ref 49. Copyright 2005, American Chemical Society)

		Reaction conditions[c]				
macrolactone[a]	catalyst[b]	drying method	temp. (°C)	time (h)	M_n[d] [Da]	M_w[d] [Da]
Mix	Sn(Oct)	toluene evaporation	135	4 + 24	1600	1800
Mix	Sn(Oct)	N_2 degassing (in bulk)	135	4 + 24	1600	1800
Mix	Sn(Oct)	high-vacuum technique	80	10	1600	1800
Mix	Y(OiPr)	high-vacuum technique	120	10	2200	2700
Mix	Y(OiPr)	high-vacuum technique	120	24	3250	4000
Mix	"zinc"	N2 degassing (in CH2Cl2)	21	3	1600	1800
Mix	"zinc"	N2 degassing (in CH2Cl2)	−71	5	298	
Mix	"zinc"	N2 degassing (in CH2Cl2)	80	1/2+ 24	1600	1800
1RM	Me_3SiONa	high-vacuum technique (in THF extra dry)	40	114	1400	1500
1RM	Sn(Oct)	toluene evaporation	135	4 + 24	280	
2RM	Sn(Oct)	toluene evaporation	135	4 + 24	4400	5700

[a]Polymerizations performed on a ricinoleic lactone mixture (mix) and purified **1RM** and **2RM**. [b]Catalysts used for polymerization: Sn(Oct), Y(OiPr), zinc catalyst (2,4-di-*tert*-butyl-6-{[(2′-dimethylaminoethyl)methylamino]methyl}phenol)ethylzinc, Me_3SiONa. [c]Reaction conditions are typical for ring-opening polymerization of lactones of 5−7 atoms. [d]Determined by GPC. The macrolactone mixture was dried by evaporating the toluene under vacuum. Polymerization was carried out in sealed glass ampules.

Scheme 17. Ring-Opening Polymerization for the Preparation of Copolyester[49]



using tinoctoate resulted in polymers M_w ∼ 5000−16000 Da and T_m ∼ 100−130 °C for copolymers containing 10−50% w/w ricinoleic acid residues (Scheme 17).

These copolymers degrade very slow, and released only ∼7% of lactic acid after 60 days; PLA released more than 20% of lactic acid. On the other hand, copolyesters containing >20%

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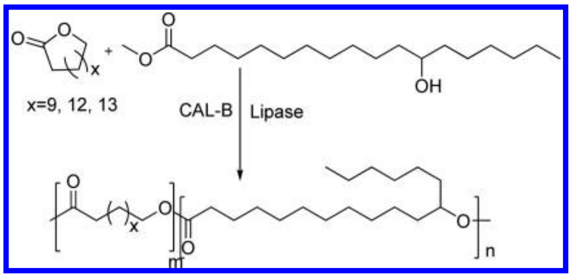
Scheme 18. Enzymatic Synthesis of Polyesters Based on 12-Hydroxystearic Acid and Macrolides[52]



w/w RA, degraded and released lactic acid faster than pure PLA, due to low crystallinity.[49]

3.3. Enzyme Catalyzed Synthesis of Polyesters. It is essential to have the polyesters uncontaminated with possible toxic metallic contaminants for biomedical applications. Enzyme catalyzed synthesis of polyesters is an alternative technique for the synthesis of metal free polyesters.[22,23] Enzymatic polyester synthesis involves several characteristic features of green chemistry.[23] In this section, we discuss a few examples of polyesters based on castor oil/ricinoleic acid.

High-molecular-weight polyricinoleate (M_w = 100600 Da) was synthesized through enzymatic (immobilized lipase from *Pseudomonas cepacia*) polycondensation of methylricinoleate at 80 °C for 7 days. The polymer is viscous at room temperature with T_g of −74.8 °C, showed no crystallinity, and biodegraded by activated sludge. This polyricinoleate was cross-linked by dicumyl peroxide with significant hardness.[50]

High M_w poly[(12-hydroxydodecanoate)-*co*-(12-hydroxystearate)] [poly(12HD-*co*-12HS)] was synthesized by polycondensing 12-hydroxydodecanoic acid and methyl 12-hydroxystearate. The reaction was catalyzed by immobilized lipase from *Candida antarctica* in toluene at 90 °C. Poly(12HD-*co*-12HS) with >60 mol % of 12HS was a viscous liquid at room temperature. They observed Young's modulus and hardness decreases with increasing the 12HS content. Poly(12HD-*co*-36 mol % 12HS) is elastic, hardness 70 A. The polymer degrades through activated sludge and metabolizes through lipase.[51]

Synthesis of a series of copolymers based on different macrolides (dodecanolidepentadecanolide, and octadecanolide) and 12-hydroxystearic acid methyl ester (12-HS) was prepared by copolymerization (M_w 140000−290000 Da) using lipase as a catalyst (Scheme 18). From the analysis of DSC and WAXS, T_m and crystalline nature decreased with increasing 12HS content, and elongation at the break point increased with increasing 12HS content. Copolymers with 40% or higher 12HS content showed excellent biodegradabilities.[52]

Star-shaped polyesters of poly(ricinoleic acid) and polyolacyl acceptors (trimethylolpropane, pentaerythritol, and dimerdiol) were reported. They were synthesized by bulk polymerization at 70 °C over a 1−2-week period (Scheme 19). This reaction was catalyzed by *C. antarctica B* lipase, and *R. miehei*. Pentaerythritol−poly(ricinoleic acid) tetraester has M_w of 4850 Da (calculated by ^{1}H NMR); 78% of the polyol hydroxyl groups were esterified. Only 17 wt % non-esterified linear poly(ricinoleic acid) was observed in the product and 83% polyol esters. The obtained product was viscous in nature and melting point temperatures below −7.5 °C. This result suggests their use as environmentally friendly biodegradable materials.[53]

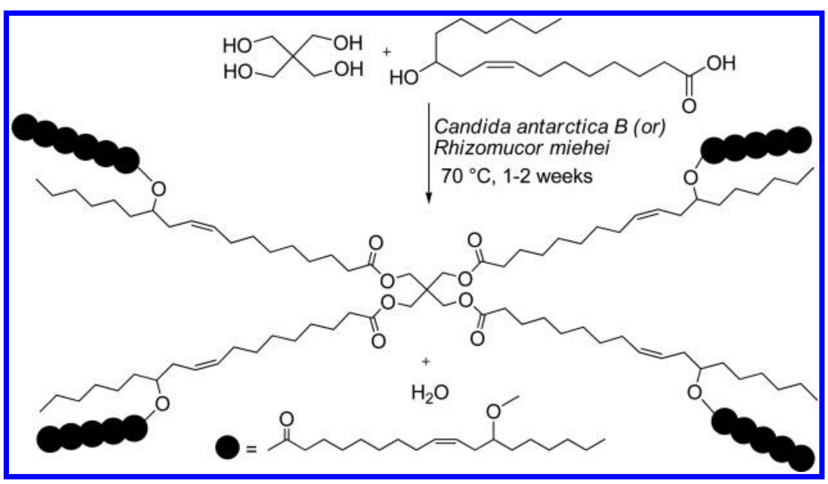
Methyl epoxyricinoleate was prepared by the lipase-catalyzed epoxidation of methyl ricinoleate with H_2O_2. High M_w (∼272 000 Da) polyepoxyricinoleate was synthesized by polycondensation, using immobilized lipase from *Burkholderiacepacia* (lipase PS-IM) in bulk at 80 °C for 5 days. Polyepoxyricinoleate showed low temperature fluidability and readily cured by maleicanhydride at 80 °C to produce a chloroform insoluble polyepoxyricinoleate-maleic acid film (Scheme 20). Both T_g and Young's modulus increased with maleic acid and polyepoxyricinoleic acid content. Elongation at break decreased with increasing maleic acid content and polyepoxyricinoleic acid. Methyl epoxyricinoleate, polyepoxyricinoleic acid, and polyepoxyricinoleate-maleic acid showed biodegradability by activated sludge (converting to simplest chemical forms like water and carbondioxide).[54]

Biobased thermosetting elastomer was prepared using methyl ricinoleate by lipase-catalyzed polymerization to obtain polyricinoleate, followed by vulcanization. The carbon black filled polyricinoleate was cured with sulfur curatives to prepare thermosetting elastomer, which was like a rubber sheet with nonsticky surface. The study findings concluded that these elastomers could replace both conventional synthetic and natural rubbers.[55]

4. BIOMEDICAL APPLICATIONS OF CASTOR OIL/RICINOLEIC ACID-BASED POLYESTERS

The hydrophobic nature of the fatty acids containing polyesters has better control over drug release properties.[49] The release

Scheme 19. Synthesis of Star Shaped Polyesters of Pentaerithritol-Tetra[Polyricinoleic acid] with Bulk Polymerization Catalyzed by Enzymes[53]



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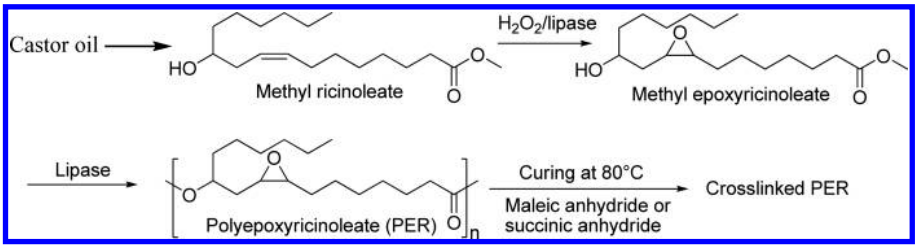
Scheme 20. Enzymatic Synthesis and Cross Linking of High Molecular Weight Polyepoxyricinoleate[54]



rates of the drugs from these polymers is controlled by the degradation of the polymer.[56] The degraded fatty acids from these polyesters are eliminated from the body by β-oxidation pathway and excreted in the form of CO_2. The use of ricinoleic acid-based polyesters in the drug release is an advantageous strategy. In addition to having two functional groups, ricinoleic acid also exhibits a combination of ananalgesic and an anti-inflammatory effect when administered topically.[57]

4.1. Toxicity Evaluation of Polyesters. Systematic toxicological studies were first conducted during 1950s and 1960s, for investigating the toxicity of polyglycerolpolyricinoleate (PGPR). Nineteen human volunteers consumed PGPR; their diet had constant fat and protein levels. The volunteer consumed up to 10 g/day PGPR in soups, cakes, and toffee bars for 2 weeks. Fat balance tests confirmed the digestion and absorption of PGPR; the polymer was found safe for human use.[58,59] PGPR was synthesized using the radiolabeled precursors. Studies were made of the absorption, tissue distribution, metabolism and excretion of these 14C- or tritium-labeled PGPR samples administered to rats. The results indicate very extensive digestion of the PGPR polymer to polyglycerols and fatty acids. The fatty acids were metabolized, and the mono-, di-, and triglycerols were absorbed from the intestinal tract and rapidly excreted unchanged in the urine, but the hexa-, penta-, and higher polyglycerols were essentially not absorbed and excreted in the fecal matter.[60]

The carcinogenic potential of the PGPR was evaluated in rats and mice. Two different groups of male and female rats and two sets of male and female mice were given purified diets containing 5% of either PGPR or groundnut oil for 2 years and 80 weeks, respectively. After the study, no carcinogenic effect of PGPR was observed, and dietary PGPR had no adverse effect on growth, food consumption, longevity, and hematology.[61]

Absorbable biomaterial containing 70% w/w RA and 30% w/w SA[P(SA-RA) 3:7] was implanted in rats to assess safety and tissue compatibility. One study reported subcutaneous (SC) intramuscularly (IM) injection. A second study reported intracranial injection. In the former study, implants were safe with no tissue damage, polymer-related lesions, or abnormalities. Initial histopathology suggested a foreign body reaction, but over the time, it showed excellent tissue repair and good tissue tolerance. In the latter study, no neurological deficits or behavior changes suggestive of systemic or localized toxicity were observed. Brain tissue parenchyma was normal in and around the edges of the implant. It was used as a scaffold for varied applications, in the localized and sustained delivery of therapeutic agents.[62]

Polyesters prepared from RA, sebacic, and citric acid with mannitol are compatible with C2C12 myoblast cells. Oriented cell growth was observed after culturing myoblast cells for 3 days. These polyesters can be used as tissue engineering scaffolds and for localized drug delivery.[31]

P(SA-RA) 3:7 copolymer subcutaneous implant in rats showed major chemical changes during the first few days (post-implantation). Anhydride bonds hydrolyze resulting in ~45% weight loss; associated with sharp decrease in the molecular weight. The polymer degrades into 2−4 oligomeric ester units of RA and then degrades to RA. The in vivo hydrolytic degradation process correlates with in vitro degradation.[63]

4.2. Polyesters as Drug Delivery Systems. Cis-platin release from the poly(ester anhydride)s was studied, in 0.1 M phosphate buffer (pH 7.4) at 37 °C. The formulations release cis-platin at an average rate of 0.45%/h for the first 73 h (Figure 1).

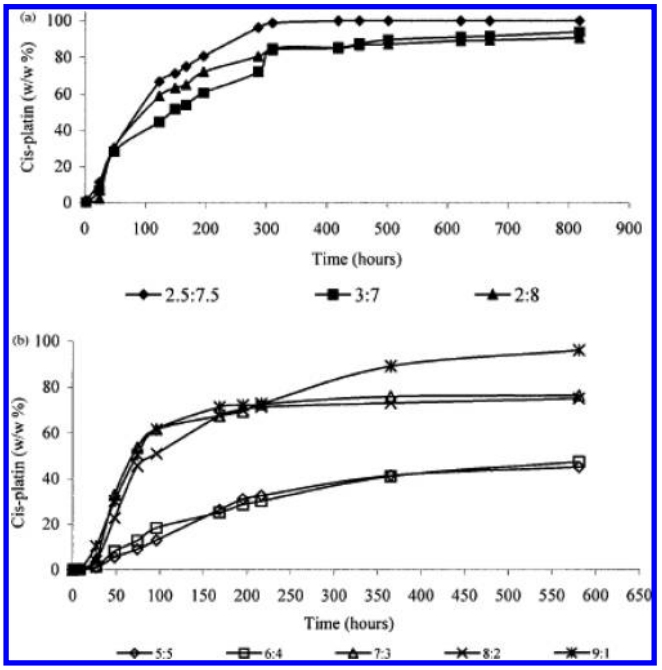


Figure 1. In vitro release of cis-platinum from poly(PSA−RA)s matrices: (a) release from liquid polymers (RA > 60%) and (b) release from solid matrices (RA < 60%). (Reproduced from ref 35. Copyright 2003 Wiley Periodicals, Inc., with permission from John Wiley & Sons.)

Release was much slower afterward due to the enhanced release of sebacic acid. This release increases the hydrophobicity of the surrounding medium. Drug release depends on the RA content of the polymer. Higher RA content slows release of the drug by solid polymer matrix (Figure 1). Polymers containing 30% RA released about 60% of the cis-platin within 100 h, whereas the 50% and 60% RA containing polymers showed only 15% release within 100 h.[35]

In vitro release of hydrophilic 5- fluorouracil (5FU) (Figure 2A) and hydrophobic drug triamcinolone (Figure 2B) from P(LA-RA)s 60:40 prepared by different methods such as condensation (COND), ring-opening polymerization (ROP), and transesterification (TRANS) was studied. Drug release by condensation of

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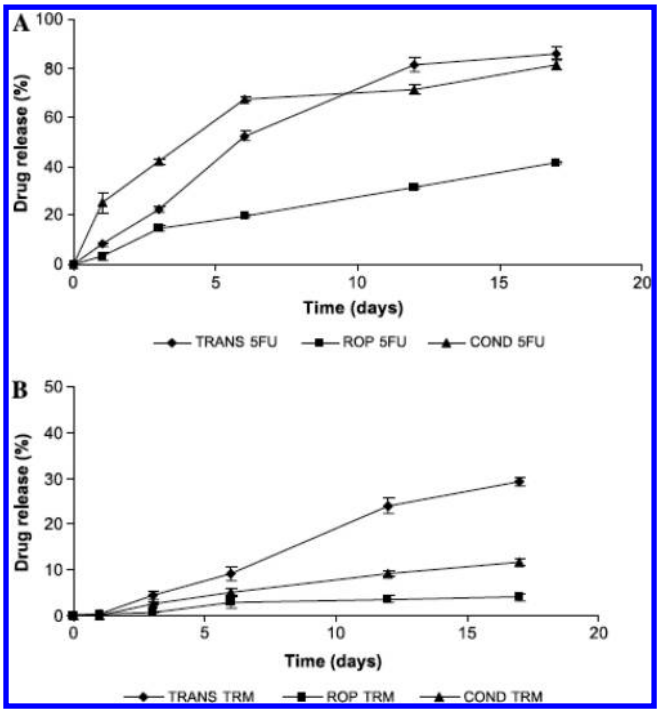

Figure 2. In vitro release of 5FU (A) and triamcinalone (B) from P(LA-RA)s 60:40 prepared by different polymerization methods. (Reproduced from ref 26, Copyright 2006. With kind permission from Springer Science and Business Media, Inc.)

the acids was faster than from pasty P(PLA-RA) 60:40 synthesized by transesterification for both drugs. However, 5FU was released faster than hydrophobic triamcinolone.[26]

Two model drugs (Gentamicin sulfate and Triamcinolone) were incorporated into the polymeric paste of poly(ester-anhydride)s at room temperature and injected into buffer phosphate solutionat 37 °C. A constant release of both drugs for over 30 days was obtained. Longer chain dicarboxylic acids resulted in a slower release. The release of the drugs from polymers prepared from RA maleate or succinate was identical.[36]

Tamoxifencitrate-loaded cylindrical polymeric implants for application at tumor sites were prepared based on poly(sebacic acid-*co*-ricinoleic-ester anhydride) 70:30 w/w, a low-melting, biodegradable, and biocompatible polymer. The percentage of drug release performed in phosphate-buffered saline (pH 7.4) at body temperature from 10 and 20 wt % drug-loaded poly-(SA-RA) 70:30 w/w, implants after 30 days was found to be 42.36 and 62.60% respectively.[64]

Güç et al., report hyper branched resin (HBR) nanoparticles synthesized from copolyesters of dipentaerythritol, dimethylol-propionic acid, and RA. These HBRs were loaded with idarubicin and tamoxifen (73−74% loading efficiencies). Tamoxifen is physically bound onto the resin, but idarubicin is chemically bound. Controlled release in lipase revealed the following: tamoxifen release for initial concentration of 2.7 μg/mg of polymer was 93%. At 8 μg/mg, it was 58% by the end of the 25th day. Release of idarubicin was poor. When MCF-7 cells were exposed to tamoxifen- and idarubicin-loaded HBR nanoparticles, cell mortality was enhanced by 109- and 4.8-fold, respectively, compared to free drugs. Drug-free particles did not have significant toxicity. Therefore, drug-loaded nanoparticles are more cytotoxic than pure drugs.[29]

Release profile tamsulosin hydrochloride (TAM) incorporated in poly(sebacic acid-*co*-ricinoleic acid) (p(SA-RA) 30:70 and 20:80) in 2−20% w/w matrix were evaluated. Formulation loaded with higher drug content in the polymer matrix released faster. Moreover, the hydrophilicity of the drug hastened hydrolysis of formulation. TAM formulations stability in p(SA-RA) 30:70 under different temperatures was evaluated. The formulations were stable for ∼6 months. The drug-loaded formulation became gel after injecting into mice at the site of injection.[65]

Poly(DL-lactic acid co castor oil) (60:40 w/w) based nanoparticles containing paclitaxel were prepared as a nano drug delivery system. SEM microphotographs of nanoparticles in the form of long, flat scales are similar to rod/bone and rose flower-like shaped nano drug delivery systems. FTIR, powder XRD, and DSC results prove that the drug is entrapped within the polymeric matrix and can be in amorphous form. A prolonged period of drug release by this nanosized delivery system was observed from the in vitro release studies.[66]

Gentamicin sulfate was incorporated into P(SA-RA; 3:7 or 2:8 ratio) paste at 10−20% w/w, and its release in buffer solution was monitored. The formulation was studied against *Staphylococcus aureus*. A constant release of gentamicin was observed for a period of 28 days (Figure 3 and Figure 4).

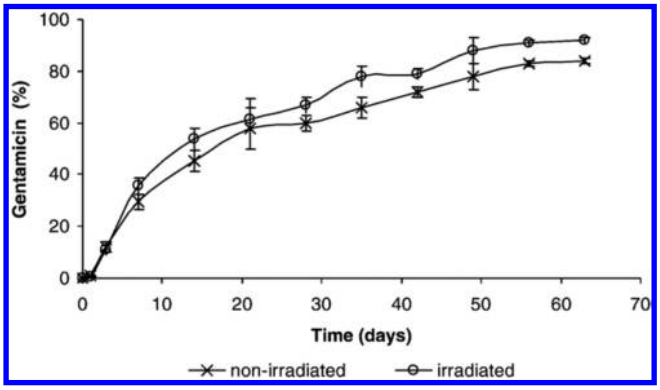

Figure 3. Gentamicin sulfate release from irradiated and nonirradiated P(SA-RA)3:7 loaded with 20% drug. (Reproduced from ref 67, Copyright 2006, with permission from Elsevier.)

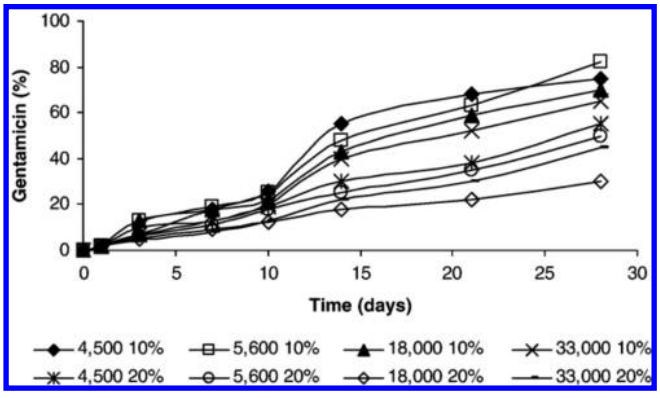

Figure 4. Release of gentamicin sulfate from P(SA-RA) 3:7 w/w with a different number molecular weight (M_n) and amount of drug. (Reproduced from ref 67, Copyright 2006, with permission from Elsevier.)

The formulations were stable to γ-irradiation sterilization, but had to be refrigerated. The toxicity evaluation of the formulations with gentamicin was examined by subcutaneous injection to rats. Four weeks after implantation, histopathological examination of

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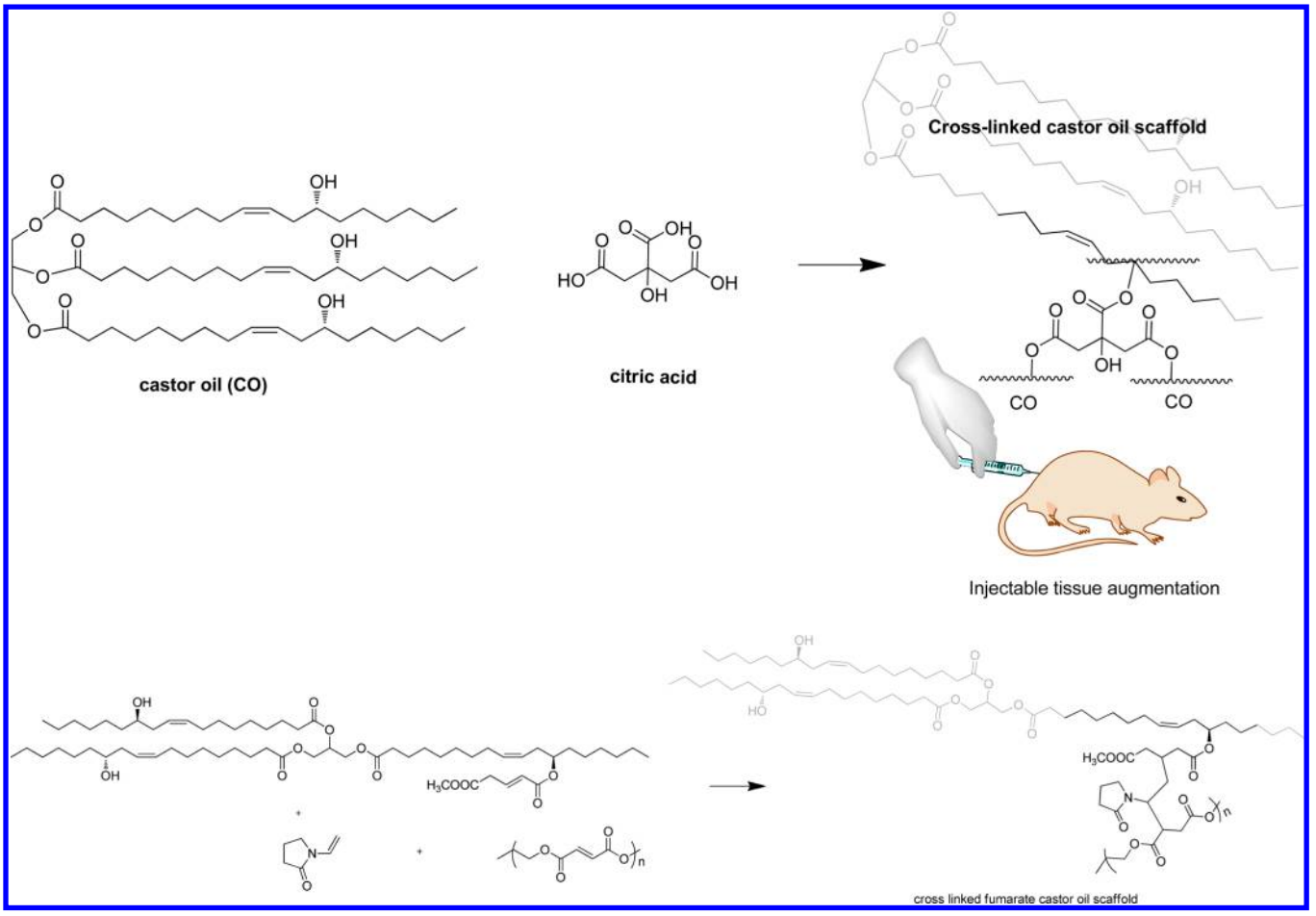

Figure 5. Examples of castor-oil-based polyesters for injectable implant system. First, a cross-linked citric acid-castor oil based material being used for tissue augmentation. Second, an orthopedic filler was developed with *in situ* cross-linkable hydroxyl terminated-poly(castor oil fumarate).

the tissues surrounding the implant showed no inflammation. It was observed from the preliminary study that P(SA-RA) 3:7 loaded with 10%−20% gentamicin sulfate can be used as an injectable biodegradable device for in situ treatment of osteomyelitis induced by *S. aureus*.[67] In most of the studies, the authors observed that these copolyesters are stable toward γ-irradiation.

Low molecular weight hydroxy fatty acid based copolymers were synthesized. Polymer degradation was observed by both surface and bulk erosion. Controlled drug release was conducted with the drugs having different aqueous solubility such as methotrexate (hydrophobic) and 5FU (hydrophilic). A negligible effect was observed for the release profiles of drug loaded at 5, 10, and 20% w/w of methotrexate. Initial inflammation was observed in the injection site, but it healed over time. The entrapped drug was released in a controlled manner from the polymers; it had biocompatibility with the tissue. Due to the injectable nature of these polymers, they have a great potential as a drug carrier for localized delivery of anticancer drugs.[68] Castor oil and citric acid copolyesters demonstrated tolerability, stability, and long persistence in vitro and in vivo with excellent tissue biocompatibility. These polymers have potential use in soft tissue augmentation.[45]

Castor oil-based poly(mannitol-citric sebacate) polyester was used as a drug carrier for the drug 5-FU. Different 5-FU loading and their release was studied in phosphate buffer saline. The cumulative release profiles revealed biphasic release−initial burst followed by complete release within 42 h. Release studies with isoniazid showed an *n*th order kinetic model. One hundred percent cumulative release was achieved after 12 days. Two model drugs, with the same polymer matrix, had different release profiles. All these data are evidence of strong interaction between the polymer and the drug.[30]

We reported a nanoparticle system for delivery of anticancer drugs using PEG-ester of RA (known a Cremophore).[69−72] Cremophor EL is prepared by the reaction of castor oil with ethylene oxide when polyethoxylated castor oil is a surface active agent. Due to its surfactant nature, this has been widely used in solublizing water insoluble drugs. Even though it is non toxic, many reports have suggested that the formulations of Cremophor EL with drugs induce serious complications such as anaphylactoid hypersensitivity, axanol swelling, degeneration, and demyelination.[73]

4.3. Polyesters in implants and Tissue Engineering. Castor oil-based polyurethanes are one of the 'materials of choice' for polymeric implants and tissue engineering scaffolds.[74] However, polyesters have long been used for this purpose.[75] On the other hand, only a few reports on castor oil based-polyesters as medical implantable devices have been reported. We recently reported castor oil−citrc acid-based injectable tissue augmentation scaffold (Figure 5).[45] Injectable cross-linked scaffolds were synthesized from castor oil and citric acid. The scaffold may be used as a filler or for augmentation purposes.

Cross-linked castor−fumarate-based sacffold has also been reported for potential use as orthopedic bone cement scaffold.

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They used vinylpyrrolidone as an in situ cross-linker of castor oil. This hydroxyl-terminated poly(castor oil fumarate) may be used as a scaffold for bone scaffold and cement. They set into three dimensionally cross-linked toughened material with a modulus of 381.088 MPa. The composite showed the desired thermal properties and hydrophilic character. The present cross-linked material exhibits cytocompatibility with L929 fibroblast cells (Figure 5).[76]

Castor oil-based polyester is generally pasty with a melting point around 37 °C. Moreover, cross-linking the double bond or the hydroxy group to yield a toughened material suitable as implant scaffold is rare. Overall, use of castor oil-based polyesters in implants is rare, but a few recent reports show it is promising and may be used in the future.

5. CONCLUSIONS AND FUTURE PERSPECTIVES

Castor oil has been known as a medicinal oil since ancient times. This oil contains bifunctional RA, which has a free hydroxyl group, ideal for esterification. In view of polymer chemistry, castor oil is considered a triol/triene monomer, ready to undergo chemical modifications.

The chemistry of castor oil has been explored in two different ways: (a) to use castor oil as a monomer, and (b) to hydrolyze castor oil and use RA as a monomer, which is unique among any other vegetable oil. Biodegradability, safety, injectability, etc. are added features. Caster oil (or RA) combined with other monomers presents a vast array of copolymers. The chemistry of these copolymers is fine-tuned to provide materials with different properties. Therefore, castor oil/RA polyesters offer a wide range of biomaterials, form solid implants to in situ injectable hydrophobic gels. Polyesters with controlled mechanical, thermal, viscoelastic, and degradation profiles can be obtained by simply changing the comonomer compositions. Common biodegradable polyesters and polyanhydrides can be modified to be more hydrophobic, cross-linked, pliable or pasty by simply copolymerization with minute amounts of castor oil or/and RA or its lactone. Overall, castor oil/RA's legacy is likely to continue, especially for drug delivery and implantation purposes.

Finally, we discuss precisely controlling the architecture of resulting RA copolyesters. Current state-of-the-art synthesis produces random or approximately block copolymers; sometimes leading to unpredictable and nonreproducible properties. A synthetic strategy that produces copolymers (block, random, or alternate) and brings a paradigm shift in polyester synthesis is needed.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Carothers, W. H. *J. Am. Chem. Soc.* **1929**, *51*, 2548−2559.
(2) Carothers, W. H.; Arvin, G. A. *J. Am. Chem. Soc.* **1929**, *51*, 2560−2570.
(3) Maisonneuve, L.; Lebarbe, T.; Grau, E.; Cramail, H. *Polym. Chem.* **2013**, *4*, 5472−5517.
(4) Vilela, C.; Sousa, A. F.; Fonseca, A. C.; Serra, A. C.; Coelho, J. F. J.; Freire, C. S. R.; Silvestre, A. J. D. *Polym. Chem.* **2014**, *5*, 3119−3141.
(5) Biermann, U.; Friedt, W.; Lang, S.; Lühs, W.; Machmüller, G.; Metzger, J. O.; Rüsch gen. Klaas, M.; Schäfer, H. J.; Schneider, M. P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2206−2224.
(6) Domb, A. J.; Nudelman, R. *J. Polym. Sci., Part A: Polym. Chem.* **1995**, *33*, 717−725.
(7) Teomim, D.; Domb, A. J. *J. Polym. Sci., Part A: Polym. Chem.* **1999**, *37*, 3337−3344.
(8) Teomim, D.; Domb, A. J. *Biomacromolecules* **2001**, *2*, 37−44.
(9) Teomim, D.; Nyska, A.; Domb, A. J. *J. Biomed.Mater. Res.* **1999**, *45*, 258−267.
(10) Mutlu, H.; Meier, M. A. R. *Eur. J. Lipid Sci. Technol.* **2010**, *112*, 10−30.
(11) Ogunniyi, D. S. *Bioresour. Technol.* **2006**, *97*, 1086−1091.
(12) Gaginella, T. S.; Phillips, S. F. *Am. J. Dig. Dis.* **1975**, *20*, 1171−1177.
(13) Scarpa, A.; Guerci, A. *J. Ethnopharmacol.* **1982**, *5*, 117−137.
(14) Nunn, J. *Ancient Egyptian Medicine*; The British Museum Press: London, 1996.
(15) Tunaru, S.; Althoff, T. F.; Nüsing, R. M.; Diener, M.; Offermanns, S. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 9179−9184.
(16) Vignolo, R.; Naughton, F. *Int. News Fats, Oils Rel. Mater. (INFORM)* **1991**, *2*, 692−699.
(17) Petrović, Z. S.; Cvetković, I.; Hong, D.; Wan, X.; Zhang, W.; Abraham, T.; Malsam, J. *J. Appl. Polym. Sci.* **2008**, *108*, 1184−1190.
(18) Sokolsky-Papkov, M.; Shikanov, A.; Kumar, N.; Vaisman, B.; Domb, A. J. *Bulletin of the Israel Chemical Society* **2008**, *23*, 12−17.
(19) Edlund, U.; Albertsson, A. C. *Adv. Drug Delivery Rev.* **2003**, *55*, 585−609.
(20) Okada, M. *Prog. Polym. Sci.* **2002**, *27*, 87−133.
(21) Braun, D.; Cherdron,H.;Rehahn, M.; Ritter,H.*Polymer Synthesis: Theory and Practice; Fundamentals, Methods, Experiments*, 4th ed.; Springer: Berlin, Heidelberg, 2004; pp 259−322.
(22) Varma, I. K.; Albertsson, A. C.; Rajkhowa, R.; Srivastava, R. K. *Prog. Polym. Sci.* **2005**, *30*, 949−981.
(23) Kobayashi, S. *Polym. Adv. Technol.* **2015**, *26*, 677−686.
(24) Slivniak, R.; Domb, A. J. *Macromolecules* **2005**, *38*, 5545−5553.
(25) Slivniak, R.; Langer, R.; Domb, A. J. *Macromolecules* **2005**, *38*, 5634−5639.
(26) Slivniak, R.; Ezra, A.; Domb, A. J. *Pharm. Res.* **2006**, *23*, 1306−1312.
(27) Paleos, C. M.; Tsiourvas, D.; Sideratou, Z. *Mol. Pharmaceutics* **2007**, *4*, 169−88.
(28) Bharathi, P.; Moore, J. S. *Macromolecules* **2000**, *33*, 3212−3218.
(29) Güç, E.; Gündüz, G.; Gündüz, U. *Drug Dev. Ind. Pharm.* **2010**, *36*, 1139−1148.
(30) Sathiskumar, P. S.; Chopra, S.; Madras, G. *Curr. Sci.* **2012**, *102*, 97−104.
(31) Chandorkar, Y.; Madras, G.; Basu, B. *J. Mater. Chem. B* **2013**, *1*, 865−875.
(32) Ristić, I.; Marinović-Cincović, M.; Cakić, S.; Tanasić, L.; Budinski-Simendić, J. *Polym. Bull.* **2013**, *70*, 1723−1738.
(33) Lebarbe, T.; Ibarboure, E.; Gadenne, B.; Alfos, C.; Cramail, H. *Polym. Chem.* **2013**, *4*, 3357−3369.
(34) Can, E.; Wool, R. P.; Küsefoğlu, S. *J. Appl. Polym. Sci.* **2006**, *102*, 1497−1504.
(35) Krasko, M. Y.; Shikanov, A.; Ezra, A.; Domb, A. J. *J. Polym. Sci., Part A: Polym. Chem.* **2003**, *41*, 1059−1069.
(36) Krasko, M. Y.; Domb, A. J. *J. Biomed. Mater. Res., Part A* **2007**, *83A*, 1138−1145.
(37) Fay, F.; Linossier, I.; Langlois, V.; Vallee-Rehel, K.; Krasko, M. Y.; Domb, A. J. *J. Appl. Polym. Sci.* **2007**, *106*, 3768−3777.
(38) Gautrot, J. E.; Zhu, X. X. *Chem. Commun.* **2008**, 1674−1676.
(39) Robertson, M. L.; Paxton, J. M.; Hillmyer, M. A. *ACS Appl. Mater. Interfaces* **2011**, *3*, 3402−3410.

DOI: 10.1021/acs.biomac.5b00923
Biomacromolecules 2015, 16, 2572−2587

(40) Sokolsky-Papkov, M.; Langer, R.; Domb, A. J. *Polym. Adv. Technol.* **2011**, *22*, 502−511.
(41) Mamat, X.; Wang, Y.; Eli, W. *Polym. Adv. Technol.* **2012**, *23*, 1271−1275.
(42) El-Ghazawy, R. A. M.; Farag, R. K.; Elsaeed, S. M.; Abde-Halim, E. -D. A.; Yossef, M. A.; Toyor, W. E. *J. Dispersion Sci. Technol.* **2014**, *35*, 350−357.
(43) Péres, E. U. X.; Souza, F.G.d., Jr; Silva, F. M.; Chaker, J. A.; Suarez, P. A. Z. *Ind. Crops Prod.* **2014**, *59*, 260−267.
(44) Jain, J. P.; Sokolsky, M.; Kumar, N.; Domb, A. J. *Polym. Rev.* **2008**, *48*, 156−191.
(45) Ickowicz, D. E.; Haim-Zada, M.; Abbas, R.; Touitou, D.; Nyska, A.; Golovanevski, L.; Weiniger, C. F.; Katzhendler, J.; Domb, A. J. *Polym. Adv. Technol.* **2014**, *25*, 1323−1328.
(46) De, B.; Gupta, K.; Mandal, M.; Karak, N. *ACS Sustainable Chem. Eng.* **2014**, *2*, 445−453.
(47) O'Lenick, A. J., Jr; LaVay, C. *Cosmet. Toiletries Mag.* **2002**, *117*, 59−64.
(48) Liu, C.; Li, J.; Lei, W.; Zhou, Y. *Ind. Crops Prod.* **2014**, *52*, 329−337.
(49) Slivniak, R.; Domb, A. J. *Biomacromolecules* **2005**, *6*, 1679−1688.
(50) Ebata, H.; Toshima, K.; Matsumura, S. *Macromol. Biosci.* **2007**, *7*, 798−803.
(51) Ebata, H.; Toshima, K.; Matsumura, S. *Macromol. Biosci.* **2008**, *8*, 38−45.
(52) Kobayashi, T.; Matsumura, S. *Polym. Degrad. Stab.* **2011**, *96*, 2071−2079.
(53) Kelly, A. R.; Hayes, D. G. *J. Appl. Polym. Sci.* **2006**, *101*, 1646−1656.
(54) Kazariya, A.; Matsumura, S. *Polymers* **2012**, *4*, 486−500.
(55) Ebata, H.; Yasuda, M.; Toshima, K.; Matsumura, S. *J. Oleo Sci.* **2008**, *57*, 315−320.
(56) Uhrich, K. E.; Cannizzaro, S. M.; Langer, R. S.; Shakesheff, K. M. *Chem. Rev.* **1999**, *99*, 3181−3198.
(57) Vieira, C.; Evangelista, S.; Cirillo, R.; Lippi, A.; Maggi, C. A.; Manzini, S. *Mediators Inflammation* **2000**, *9*, 223−228.
(58) Wilson, R.; Smith, M. *Food Chem. Toxicol.* **1998**, *36*, 743−745.
(59) Wilson, R.; van Schie, B. J.; Howes, D. *Food Chem. Toxicol.* **1998**, *36*, 711−718.
(60) Howes, D.; Wilson, R.; James, C. T. *Food Chem. Toxicol.* **1998**, *36*, 719−738.
(61) Smith, M. R.; Wilson, R.; Hepburn, P. A. *Food Chem. Toxicol.* **1998**, *36*, 747−754.
(62) Vaisman, B.; Motiei, M.; Nyska, A.; Domb, A. J. *J. Biomed. Mater. Res., Part A* **2010**, *92A*, 419−431.
(63) Vaisman, B.; Ickowicz, D. E.; Abtew, E.; Haim-Zada, M.; Shikanov, A.; Domb, A. J. *Biomacromolecules* **2013**, *14*, 1465−1473.
(64) Hiremath, J. G.; Kusum Devi, V.; Devi, K.; Domb, A. J. *J. Appl. Polym. Sci.* **2008**, *107*, 2745−2754.
(65) Havivi, E.; Farber, S.; Domb, A. J. *Polym. Adv. Technol.* **2011**, *22*, 114−118.
(66) Hiremath, J. G.; Rajeshkumar, A.; Ickowicz, D.; Domb, A. J. *J. Drug Delivery Sci. Technol.* **2013**, *23*, 439−444.
(67) Krasko, M. Y.; Golenser, J.; Nyska, A.; Nyska, M.; Brin, Y. S.; Domb, A. J. *J. Controlled Release* **2007**, *117*, 90−96.
(68) Jain, J. P.; Modi, S.; Kumar, N. *J. Biomed. Mater. Res., Part A* **2008**, *84A*, 740−752.
(69) Bekerman, T.; Golenser, J.; Domb, A. *J. Pharm. Sci.* **2004**, *93*, 1264−1270.
(70) Pawar, R.; Shikanov, A.; Vaisman, B.; Domb, A. J. *Curr. Med. Chem.* **2004**, *11*, 397−402.
(71) Avramoff, A.; Khan, W.; Ezra, A.; Elgart, A.; Hoffman, A.; Domb, A. J. *J. Controlled Release* **2012**, *160*, 401−406.
(72) Hiremath, J.; Rajeshkumar, A.; Ickowicz, D.; Domb, A. J. *J. Drug Delivery Sci. Technol.* **2013**, *23*, 439−444.
(73) Tabarelli, Z.; Berlese, D.; Sauzem, P.; Mello, C.; Rubin, M. *Bra.J. Med.Biol. Res.* **2003**, *36*, 119−123.
(74) Dong, Z.; Li, Y.; Zou, Q. *Appl. Surf. Sci.* **2009**, *255*, 6087−6091.
(75) Holland, S. J.; Tighe, B. J.; Gould, P. L. *J. Controlled Release* **1986**, *4*, 155−180.
(76) Mitha, M.; Jayabalan, M. *J. Mater. Sci.: Mater. Med.* **2009**, *20*, 203−211.

DOI: 10.1021/acs.biomac.5b00923
Biomacromolecules 2015, 16, 2572−2587