

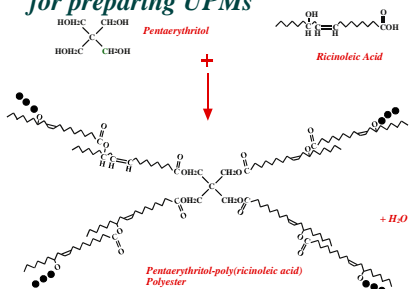
Objective

Preparation of Unimolecular Polymeric Micelles, UPMs (apolar core; polar “corona”) for drug delivery using solvent-free biocatalysis

1st Generation Star Polymers

Sub-Objective: Star polymers synthesized from lipase-catalyzed esterification of polyols possessing primary OH groups and *oligo*(hydroxy fatty acids)

Useful as viscosity index modifiers (lubrication) and as building blocks for preparing UPMs



2-Step “Green” Synthesis (no solvents)

1. Oligomerization of ricinoleic acid (Bulk polymerization, 80°C, immobilized *Candida antarctica* lipase, CAL, from Novozymes, Inc.)
2. Attachment of *oligo*(ricinoleic acid) to acyl acceptor (Bulk polymerization, 80°C, immobilized *C. antarctica* or *Rhizomucor miehei* lipase. RML, from Novozymes, Inc.)

Molecular weight of ~5000 (GPC, NMR)

Viscosity of 2.3 Pa s, viscosity index of 155 → good properties as a lubricant additive

PEGylation of pendant -OH groups: drug delivery vehicle

April R. Kelly and Douglas G. Hayes, 2006, *J. Appl. Poly. Sci.*, 101:1646-1656

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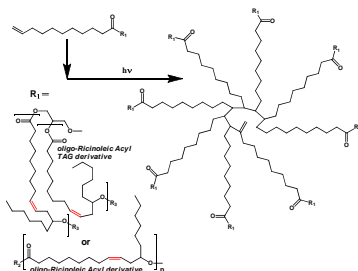
2nd Generation Star Polymers

Sub-Objectives:

1. Increase density of *oligo*(hydroxy acids) emanating from core
2. Enable more robust method of covalent attachment for hydrophilic core (e.g., PEG, polyglycerol)

General Approach

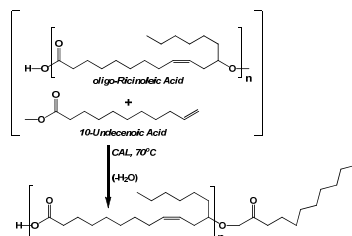
Covalent attachment of 10-undecenoic acid (UA) to *oligo*(ricinoleic acyl) derivatives; former’s terminal double bond in polymerizable in self-assembly media (Scheme I)



Scheme I: Production of UPMs via free radical polymerization of the terminal double bond of undecenoic acyl groups. R₂ and R₃ represent polar groups to provide the UPMs with a hydrophilic corona. R₁ is an amino-, or hydroxyl-terminated derivative of polyethylene glycol (PEG), polyglycerol, or polyvinyl alcohol. R₃ is a carboxylic acid-functionalized derivative of PEG or other acid-functionalized polar group.

For further information: Hayes, D.G., et al, 2012, *Polymers* 4:1037-1055

A. Covalent attachment of 10-undecenoic acid (UA) to *oligo*(ricinoleic acid) (*oligo*-RA), Scheme II



Scheme II: Lipase-catalyzed solvent-free synthesis of *oligo*-ricinoleic acid containing a covalently attached 10-undecenoic acyl group at its -OH terminus. CAL refers to immobilized *Candida antarctica* lipase.

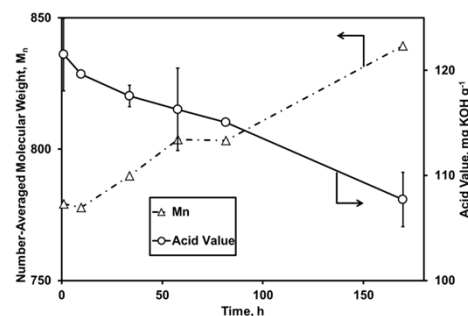
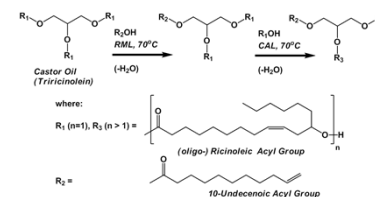


Figure 1. Analysis of CAL-catalyzed esterification of *oligo*-ricinoleic acid and 10-undecenoic acid (Scheme II). Number-averaged molecular weight (M_n), obtained from GPC and acid value (AV) versus time. Reaction conditions: 10-undecenoic acid / *oligo*-ricinoleic acid 0.20 g g⁻¹ (0.32 mol mol⁻¹); 7.1 % w/w CAL, 69°C.

Results

- 28% Conversion for UA (12% free UA in product), Fig. 1
- No chain scission of *oligo*-Ricinoleic acid (NMR analysis)
- Acid-functionalized PEG, or other hydrophilic group, can be attached to terminal OH groups

B. Covalent attachment of UA to *oligo*-RA-TAG, Scheme III



Scheme III: Lipase-catalyzed solvent-free synthesis of *oligo*-ricinoleyl, undecenoyl structured triacylglycerol (TAG) via a two-step procedure.

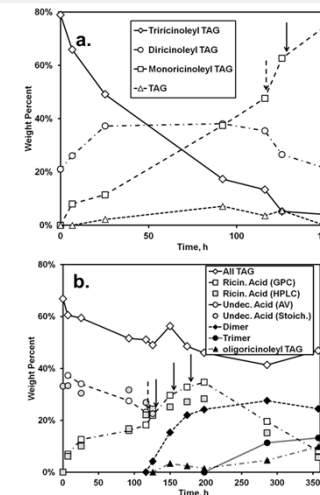


Figure 2. Time course of reaction for Scheme III. (a) change in distribution of TAG species for first step; (b) change in concentration of TAG, fatty acid, and oligomer (via HPLC)

Results

- Acidolysis of triricinolein by UA (Step 1) occurred readily; however, di- and tri-undecenoic acyl TAG formed significantly, due to acyl migration (Fig 2a).
- Hydrolysis or polymerization did not occur for Step 1 (GPC and NMR analyses)
- Step 2: Formation of *oligo*(ricinoleic acid), a side-reaction, predominated early; during latter stages, desired *oligo*-ricinoleic acyl-containing TAG formed (Fig 2b).