RESEARCH ARTICLE

Biobased Hyperbranched Poly(ester)s of Precise Structure for the Release of Therapeutics

Authors
Bob A. Howell[1], Tracy Zhang[1,2] and Patrick B. Smith[2]

Affiliations
[1]Center for Applications in Polymer Science
Department of Chemistry
Central Michigan University
Mt. Pleasant, MI 48859

[2]Michigan State University, St. Andrew Campus
1910 W. St. Andrew Rd.
Midland, MI 48640

Correspondence
Bob A. Howell
Email: howel1ba@cmich.edu

ABSTRACT

Hyperbrached poly(ester)s derived from naturally-occurring biomonomers may serve as excellent platforms for the sustained-release of therapeutics. Those generated from glycerol are particularly attractive. Traditionally, the difference in reactivity of the hydroxyl groups of glycerol has precluded the formation of well-defined polymers at high monomer conversion without gelation. Using the Martin-Smith model to select appropriate monomer ratios (ratios of functional groups), polymerization may be carried out to high conversion while avoiding gelation and with the assurance of a single type of endgroup. Various agents may be attached via esterification, amide formation or other process. Sustained release of the active agent may be readily achieved by enzyme-catalyzed hydrolysis.

INTRODUCTION

Sustained release of therapeutic agents from biocompatible delivery systems remains an area of intense interest and activity.[1,2] The controlled release of therapeutic agents from polymeric prodrugs offers several advantages, including maintenance of optimum dosage level and extended effectiveness, over conventional methods of administration. The most attractive polymeric carrier materials are biocompatible, biodegradable compounds of well-defined structure.[3,4] Hyperbranched polymers are generally superior to linear analogs as carrier platforms.[5] For similar molecular weights, the hyperbranched materials offer lower viscosity, greater solubility and a wealth of reactive endgroups for the attachment of active agents.[6] In particular, hyperbranched poly(ester)s derived from readily-available, nontoxic biomonomers are attractive as a base for the generation of sustained-release compositions. These materials may be prepared by polycondensation of a multifunctional alcohol with a multifunctional carboxylic acid. If carried out to high monomer conversion this process leads to gelation and has long been used in the coatings industry. However, for use in the preparation of sustained-release formulations, gelation must be avoided. For monomers containing functional groups of equal reactivity, e.g. pentaerythritol and a diacid, Flory-Stockmayer theory can be used to determine the ratio of monomers that may be used to achieve high monomer conversion without gelation.[7-10] However, this approach is unsuitable for polymerization of monomers containing functionality of unequal reactivity. For a variety of reasons, including widespread availability from transesterification of triglyceride to generate biodiesel, glycerol has often been used as the alcohol component in hyperbranched poly(ester) synthesis. Glycerol contains three hydroxyl groups, two primary of one reactivity in esterification and a secondary hydroxyl group of lower reactivity (the primary hydroxyl groups of glycerol are approximately 1.4 times as reactive in esterification as is the secondary hydroxyl group). Further, esterification of one hydroxyl group influences the reactivity of those remaining. For this situation, traditional gelation theory is inadequate for predicting ratios of monomers (ratios of reactive functional groups) that will permit the formation of nongelled polymers at high monomer conversion. A new approach is required. Generally, glycerol hyperbranched poly(ester)s have been produced using empirical methods—varying monomer concentration, reaction temperature or extent of reaction. This approach is unsatisfactory. In particular, polymers obtained by limiting the extent of reaction contain reactive endgroups of different types (hydroxyl and carboxyl). Further reaction is possible and on storage these materials usually gel.[11-15] These empirical methods do not permit the targeting of molecular weight, degree of branching or endpoint identity from initial reactant stoichiometry. Fortunately, this situation has been remedied by the development of the Martin-Smith model for controlled polymerization of multifunctional monomers containing functionality of different

reactivity.[16] This model is based on Macosko-Miller statistical probability and accounts for both differences in functional group reactivity and changes in reactivity as a consequence of partial substitution.[17-19] It has been verified experimentally and used to predict ratios of reactants to permit polymerization to high degrees of monomer conversion without gelation. These materials have well-defined structure and a single type of endgroup. Gelation does not occur on storage. This approach has been utilized for the preparation of structurally-precise polymers to serve as platforms for the development of useful sustained-release compositions.[20,21]

RESULTS AND DISCUSSION

Polymeric materials that are biocompatible and biodegradable are being widely utilized as platforms for the formulation of sustained-release compositions containing a variety of active agents.[22] Hyperbranched polymers often display good solubility and offer a wealth of reactive terminal groups for the attachment of therapeutic agents. Hyperbranched poly(ester)s derived from naturally-occurring, nontoxic monomers may be particularly useful for the construction of sustained-release formulations.[21, 23] Because of its abundance, widespread availability and modest cost, glycerol is commonly used as the alcohol component of hyperbranched poly(ester) synthesis.[11-16] A variety of dicarboxylic acids may be used in the preparation.[20] Perhaps the most useful is adipic acid.[16] Both glycerol and adipic acid are available from biosources and have long been recognized as safe by the U.S. Food and Drug Administration. Using the Martin-Smith model for the selection of appropriate reactant stoichiometry, polymerization may be carried out to high conversion without gelation to provide materials with well-defined structure and single endgroup functionality (Figure 1)[16]. A variety of therapeutic agents may be attached via esterification using the terminal hydroxyl groups.[21]

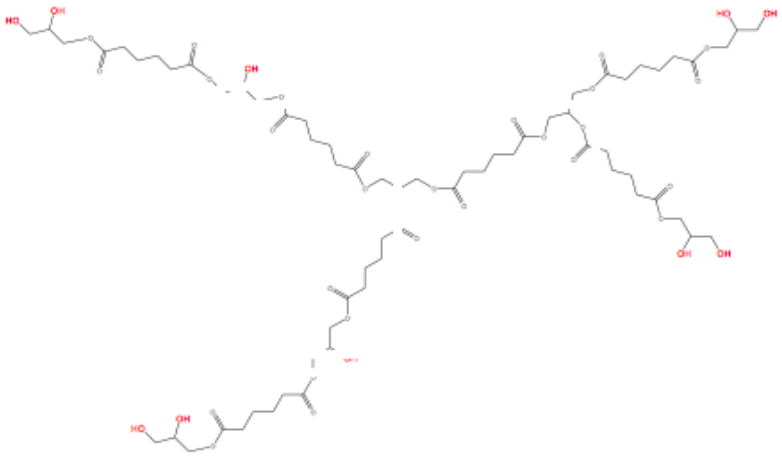
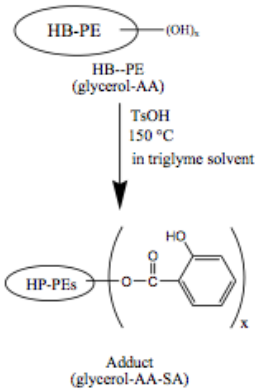


Figure 1. Glyerol/Adipic Acid Hyperbranched Poly(ester) Containing Hydroxyl Terminal Groups.

A simple example is the attachment of salicylic acid as illustrated in Scheme 1.



Scheme 1. Attachment of Salicylic Acid to the Periphery of a Hydroxyl-Terminal Glycerol/Adipic Acid Hyperbranched Poly(ester).

A stable conjugate is obtained. Release of salicylic acid may be readily achieved under the influence of enzymatic catalysis (rat liver microsomes).[21] The release rate is depicted in Figure 2.

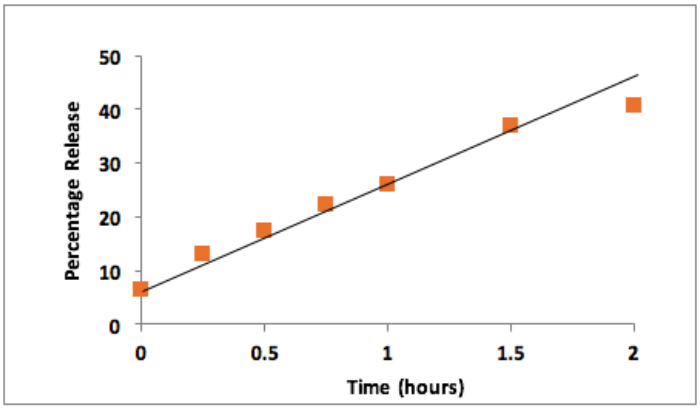


Figure 2. Release of Salicylic Acid from the Glycerol/Adipic Acid Hyperbranched Poly(ester) Conjugate.

CONCLUSIONS

Glycerol-derived hyperbranched poly(ester)s of well-defined structure and a single type of endgroup may serve as excellent platforms for the sustained-release of therapeutics. Using the Martin-Smith model to select appropriate monomer ratios, polymerization may be carried out to high conversion without gelation and the assurance of a single endgroup functionality (hydroxyl or carboxyl). Active agents may be attached by esterification (or other for carboxyl terminal polymers). Therapeutic agents may be smoothly released in a sustained manner by enzyme-catalyzed hydrolysis.

REFERENCES:

(1) J. Wang, H. Zhang, J. Xu, H. Qian, R. Liu, Z. Xu and H. Zhu, "Sustained-release Ibuprofen Prodrug Particle: Emulsifier and Initiator Regulate the Diameter and Distribution", *J. Appl. Polym. Sci.*, **2020**, doi.org/110.1002/app.49779

(2) B. Demirdirek and K. E. Uhrich, "Novel Salicylic Acid-based Chemically Crosslinked pH-Sensitive Hydrogels as Potential Drug Delivery Systems", *Int. J. Pharm.*, **2017**, 528, 406-415.

(3) B. A. Howell and D. Fan, "Poly(amidoamine) Dendrimer-supported Organoplatinum Antitumor Agents", *Proc. R. Soc. A*, **2010**, 466, 1515-1526.

(4) S. Tang, S. M. June, B. A. Howell and M. Chai, "Synthesis of Salicylate Dendrimer Prodrugs", *Tetrahedron Lett.*, **2006**, 47, 7671-7675.

(5) Y. Hed, Y. Zhang, O. C. J. Andren, X. Zeng, A. M. Nystrom and M. Malkoch, "Side-by-side Comparison of Dendritic-linear Hybrids and their Hyperbranched Analogs as Micellar Carriers of Chemotherapeutics", *J. Polym. Sci., Part A: Polym. Chem.*, **2013**, 51, 3992-3996.

(6) D. Yan, C. Cao and H. Frey, Eds., Hyperbranched Polymers: Synthesis, Properties, and Applications, John Wiley and Sons, Inc., Hoboken, NJ, **2011**.

(7) H. R. Kricheldork and G. Behnken, "Biodegradable Hyperbranched Aliphatic Polyesters Derived from Pentaerythritol", *Macromolecules*, **2008**, 41, 5651-5657.

(8) P. J. Flory, "Molecular Size Distribution in Three-dimensional Polymers. VI. Branched Polymers Containing A-R-Bf-1 Type Units", *J. Am. Chem. Soc.*, **1952**, 74, 2718-2723.

(9) W. H. Stockmayer, "Theory of Molecular Size Distribution and Gel Formation in Branched-chain Polymers", *J. Chem. Phys.*, **1943**, 11, 45.

(10) W. H. Stockmayer, "Theory of Molecular Size Distribution and Gel Formation in Branched Polymers. II. General Crosslinking", *J. Chem. Phys.*, **1944**, 12, 125.

(11) J.-F. Stumbe and B. Bruchmann, "Hyperbranched Polyesters Based on Adipic Acid and Glycerol", *Macrol. Rapid Commun.*, **2004**, 25, 921-924.

(12) V. T. Wyatt, "Lewis Acid-catalyzed Synthesis of Hyperbranched Polymers Based on Glycerol and Diacids in Toluene", *J. Am. Oil Chem. Soc.*, **2012**, 89, 313-319.

(13) V. T. Wyatt and G. D. Strahan, "Degree of Branching in Hyperbranched Poly(glycerol-co-diacid)s Synthesized in Toluene", *Polymer*, **2012**, 4, 396-407.

(14) Y. Li, W. D. Cook, C. Moorhoff, W.-C. Huang and Q.-Z. Chen, "Sythesis, Characterization and Properties of Biocompatible Poly(glycerol sebacate) Prepolymer and Gel", *Polym. Int.*, **2013**, 62, 534-547.

(15) Y. Yang, W. Lu, J. Cai, Y. Hou, S. Ouyang, W. Xie and R. A. Gross,

"Poly(oleic acid-co-glycerol): Comparison of Polymer Structure Resulting from Chemical and Lipase Catalysis", *Macromolecules*, **2011**, 44, 1977-1985.

(16) T. Zhang, B. A. Howell, A. Dumitrascu, S. J. Martin and P. B. Smith, "Synthesis and Characterization of Glycerol-Adipic Acid Hyperbranched Poly(ester)s", *Polymer*, **2014**, 55, 5065-5072.

(17) C. W. Macosko and D. R. Miller, "A New Derivation of Average Molecular Weights of Nonlinear Polymers", *Macromolecules*, **1976**, 9, 199-206.

(18) D. R. Miller and C. W. Macosko, "Average Property Relations for Nonlinear Polymerization with Unequal Reactivity," *Macromolecules*, **1978**, 11, 656-662.

(19) D. R. Miller and C. W. Macosko, "Substituent Effects in Property Relations for Stepwise Polyfunctional Polymerization", *Macromolecules*, **1980**, 13, 1063-1069.

(20) T. Zhang, B. A. Howell, and P. B. Smith, "Rational Synthesis of Hyperbranched Poly(ester)s", *Ind. Eng. Chem. Res.*, **2017**, 56, 1661-1670.

(21) T. Zhang, B. A. Howell, D. Zhang, B. Zhu, and P. B. Smith, "Hyperbranched Poly(ester)s for Delivery of Small Molecule Therapeutics", *Polym. Adv. Technol.*, **2018**, 29, 2352-2363.

(22) A. Muniandy, C. S. Lee, W. H. Lim, M. R. Pichika and K. K. Mak, "Hyperbranched Poly(glycerol esteramide): A Biocompatible Drug Carrier From Glycerol Feedstock and Dicarboxylic Acid", *J. Appl. Polym. Sci.*, **2020**, doi.org/110.1002/app.50126.

(23) B. A. Howell, T. Zhang and P. B. Smith, "Hyperbranched Poly(ester)s from Renewable Biomonomers by Design: Nontoxic Platforms for the Delivery of Therapeutic Agents", *Sci. J. Research & Rev.*, **2019**, 2(2).

