Available online at www.sciencedirect.com
ScienceDirect
Advanced Drug Delivery Reviews 60 (2008) 1056–1076
Advanced DRUG DELIVERY Reviews
www.elsevier.com/locate/addr

Recent advances in the synthesis of aliphatic polyesters by ring-opening polymerization ☆

Christine Jérôme *, Philippe Lecomte

Center for Education and Research on Macromolecules, University of Liege, B6 Sart-Tilman, B-4000 Liege, Belgium

Received 2 August 2007; accepted 14 February 2008
Available online 26 February 2008

Abstract

Advanced drug delivery systems rely on the availability of biocompatible materials. Moreover, biodegradability is highly desirable in the design of those systems. Consequently, aliphatic polyesters appear as a class of promising materials since they combine both properties. Nevertheless, their use in practical biomedical systems relies on clinical approval which not only depends on the material itself but also on its reproducible synthesis with the absence of residual toxics. The first sections of this review aim at reporting on the evolution of the initiators/catalytic systems and of the synthesis conditions (particularly the use of supercritical CO_2 as polymerization medium) in order to produce aliphatic polyesters with controlled macromolecular parameters by still "greener" ways. In addition, the further development of delivery systems also depends on the synthesis of materials exhibiting novel properties, such as amphiphilicity or pH-sensitivity that are emerging from the active research in macromolecular engineering. Functionalizing aliphatic polyesters is quite tedious due to their sensitivity towards hydrolytic degradation. The last section of this review is discussing several strategies to obtain functional (co)polyesters of various architectures providing them with novel properties.

Keywords: Aliphatic polyesters; Ring-opening polymerization; Enzymatic polymerization; Supercritical carbon dioxide

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Design and Development Strategies of Polymer Materials for Drug and Gene Delivery Applications".

* Corresponding author. Tel.: +32 4 366 34 91; fax: +32 4 366 34 97.
E-mail address: c.jerome@ulg.ac.be (C. Jérôme).

0169-409X/$ - see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.addr.2008.02.008

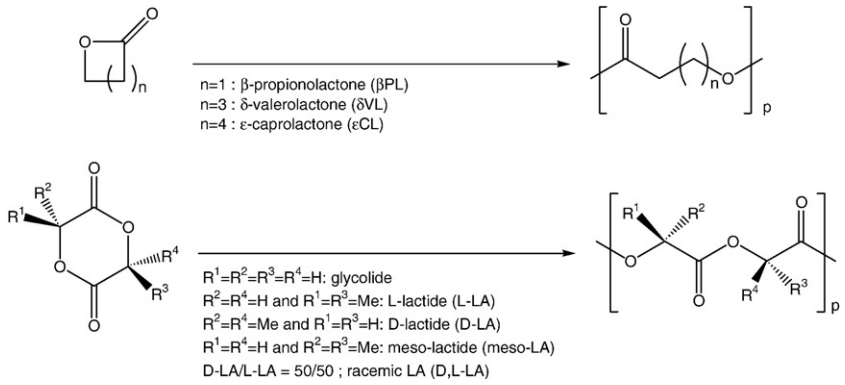
1. Introduction

The current development of nano-medicine and particularly polymeric drug delivery systems (DDS) is timely with the advances in understanding the disease-related mechanisms. This relies on the development of novel polymeric architectures and appropriate synthetic methodologies to tailor their physico-chemical properties. However, even if synthetic polymer-based drug delivery systems have been applied in drug delivery for the last 50 years, there are few examples of these macromolecules being used successfully in clinics. Even if the clinical approval of these new materials can seem to be a long way, it is worth to have a look on them and persevere investigating their production by cleaner, more efficient and less expensive ways.

Most of the synthetic polymer DDS are based on biodegradable and biocompatible materials mainly aliphatic polyesters, polyanhydrides, polyethers, polyamides, polyorthoesters and polyurethanes. The present review is going to focus on the family of aliphatic polyesters (Scheme 1). In the first section, we discuss the synthetic strategies evolution of these biodegradable polymers by focusing on the ring-opening polymerization (ROP) mechanism. Indeed, this mechanism allows quite good control of the polymer characteristics (i.e., predictable molecular weight, narrow molecular weight distribution) and is particularly well-suited for macromolecular engineering with the production of homo- and copolymers of various architectures (i.e., palm-tree, diblock, multiblock, star) (Scheme 2). The key role of tin and aluminum alkoxides as initiators of the ring-opening polymerization of lactones, lactides and glycolide will be emphasised. Then the appearance of novel less toxic or more efficient organometallics will be shortly discussed. Since the contamination of the aliphatic polyesters by potentially toxic metallic residues is particularly a concern as far as biomedical applications are envisioned, the possibility to replace organometallic initiators by lipases and full organic systems will finally be described. The second section will be dedicated to the valuable use of supercritical carbon dioxide as novel medium for the ring-opening polymerization. Purification and processing as particles of aliphatic polyesters will also be mentioned. The last section will focus on some emergent synthetic reactions particularly promising for the macromolecular engineering of aliphatic polyesters with a particular attention paid to the synthesis of amphiphilic copolymers that are promising materials for advanced DDS.

2. Synthesis of aliphatic polyesters by living/controlled ROP

The development of reproducible and efficient DDS requires the fine tailoring of the properties of the used synthetic polymers. As far as aliphatic polyesters are concerned, the control of their biodegradation rate, bioadherence, hydrophilicity, glass transition temperature and crystallinity are of the utmost importance and relies on the availability of suitable synthetic process. Aliphatic polyesters such as poly-ε-caprolactones, polylactides, and polyglycolides can be prepared by two distinct mechanisms: (i) the step-growth polymerization or polycondensation, and (ii) the ring-opening polyaddition (chain



Scheme 1. Ring-opening polymerization of unsubstituted lactones, lactides, and glycolide.