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Review Article

Polydioxanone-based bio-materials for tissue engineering and drug/gene delivery applications

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ABSTRACT

Since the commercialization of polydioxanone (PDX) as a biodegradable monofilament suture by Ethicon in 1981, the polymer has received only limited interest until recently. The limitations of polylactide-*co*-glycolide (PLGA) coupled with the growing need for materials with enhanced features and the advent of new fabrication techniques such as electrospinning have revived interest for PDX in medical devices, tissue engineering and drug delivery applications. Electrospun PDX mats show comparable mechanical properties as the major structural components of native vascular extracellular matrix (ECM) i.e. collagen and elastin. In addition, PDX's unique shape memory property provides rebound and kink resistance when fabricated into vascular conduits. The synthesis of methyl dioxanone (MeDX) monomer and copolymers of dioxanone (DX) and MeDX have opened up new perspectives for poly(ester-ether)s, enabling the design of the next generation of tissue engineering scaffolds for application in regenerating such tissues as arteries, peripheral nerve and bone. Tailoring of polymer properties and their formulation as nanoparticles, nanomicelles or nanofibers have brought along important developments in the area of controlled drug or gene delivery.

This paper reviews the synthesis of PDX and its copolymers and provides for the first time an exhaustive account of its applications in the (bio)medical field with focus on tissue engineering and drug/gene delivery.

1. Introduction

Biodegradable aliphatic polyesters such as poly(lactide) (PLA), poly(lactide-*co*-glycolide) (PLGA) and polycaprolactone (PCL) have attracted much interest for applications ranging from medical implants, bone fixation parts, scaffold fabrication, controlled drug release devices to sustained release systems for pesticides and fertilizers [1,2]. The major advantage with their use is that their degradation products can be removed by natural metabolic pathways. Generally, the copolymer PLGA is preferred compared to its constituent homopolymers for the fabrication of bone substitute constructs mainly because PLGA offers superior control of degradation properties by varying the ratio of LA and GA monomers. PLGA has a wide range of degradation rates, governed by the composition of chains, both hydrophobic/hydrophilic balance and crystallinity [3]. The possibility of controlling polymeric degradation rates allows matching with tissue regeneration rate for tissue engineering applications and control of drug release kinetics for drug delivery.

Unlike poly(ester)s, the biodegradable poly(ester-ether) PDX has not been much investigated since its introduction on the market in 1981 by Ethicon and is best known for its clinical use as a monofilament suture [4]. More recently, it has been used in the fabrication of rings for pediatric mitral and tricuspid heart valve repair [5,6] and as plates for orbital floor reconstruction [7]. Several studies have investigated the use of PDX stents in both vascular and non-vascular organs such as esophagus, trachea and intestine [8–12].

PDX shows several interesting unique properties compared to polyesters. For instance, as shown by Boland et al. [13], bulk material properties of electrospun PDX are of the same order of magnitude as the major structural components of native vascular ECM, in particular collagen and elastin. In addition, PDX has shape memory, and hence its fabrication into vascular conduits provides rebound and kink resistance [13]. However, the shape memory property of PDX makes knot retention difficult and hence undesirable when used as PDS® suture. Copolymerization with new dioxanone (DX) analogues has made it possible to modulate degradation rate compared to PDX and has opened up new perspectives for drug and gene delivery applications.

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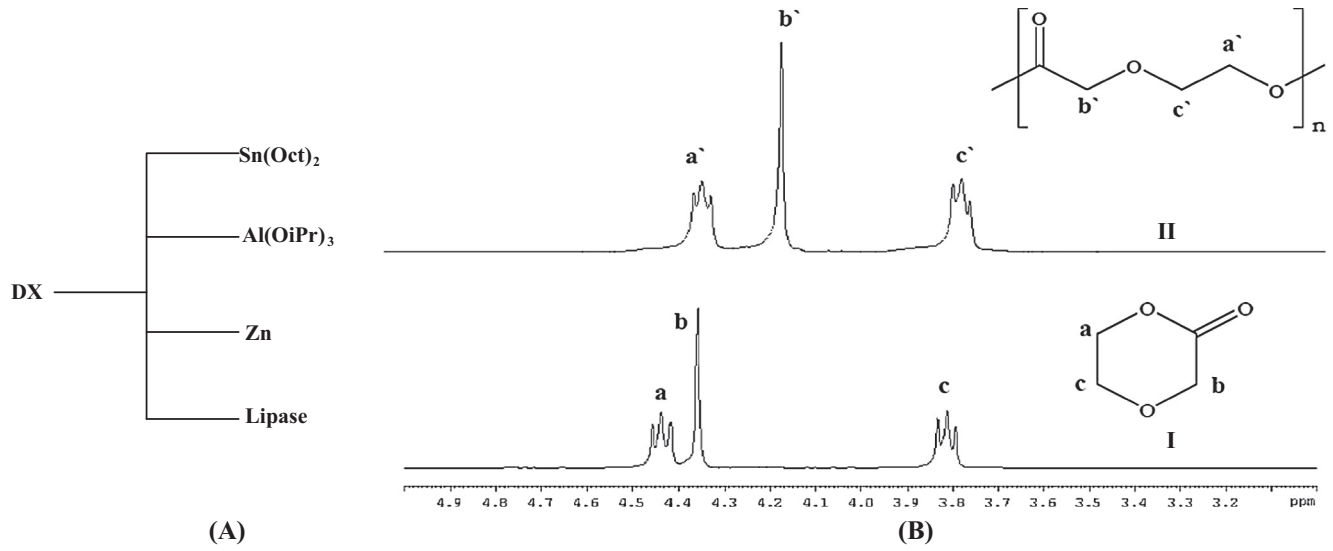

Fig. 1. (A) Different catalysts used for DX homopolymerization and (B) ^{1}H NMR spectra ($CDCl_3$) of DX (I) and PDX (II).

This paper reviews PDX-based biomaterials and their applications in tissue engineering and drug/gene delivery. An introductory overview of the synthesis of DX monomer and its methyl derivative (MeDX) as well as their homopolymers and copolymers is given while the focus will be on their use as scaffolds for tissue engineering applications as well as for the elaboration of drug delivery devices.

2. Synthesis of DX and its derivatives

The synthesis of DX was first reported by Doddi et al. [14] who reacted sodium glycolate with chloroacetic acid. The resulting hydroxy acid undergoes cyclization at 200 °C in the presence of $MgCO_3$, to yield 1,4-dioxan-2-one (DX). The crude product was purified to 99% by multiple crystallization and distillation with 50–70% yield. In an attempt to improve on yield, Nakatami et al. [15] purified the sodium salt of the hydroxy acid to eliminate ethylene glycol and any residual chloroacetic acid or chloroacetate. However, the yield of the product (67%) did not improve significantly.

A one-step synthesis was described by Forschner et al. [16] whereby oxidative dehydrogenation of diethylene glycol is performed in the presence of copper oxide catalysts supported on silica particles at 275 °C under hydrogen atmosphere. However, the exact reaction conditions and preparation of the catalyst still remain buried in patents.

More recently, the synthesis of a dioxanone analogue namely D,L-3-methyl-1,4-dioxanone (MeDX) [17,18] was reported. The monomer was synthesized using a modified version of Doddi's method (Scheme 1). Briefly, sodium glycolate was made to react with D,L-2-chloropropionic acid. Intramolecular esterification of the hydroxyl acid was performed in the presence of dicyclohexylcarbodiimide (DCC) as a catalyst. Purified MeDX monomer was obtained by cryodistillation in approximately 50% yield.

2.1. Homopolymerization of DX and MeDX

Polydioxanone (PDX) is synthesized by ring-opening polymerization (ROP) of DX. The catalyst plays an important role in the polymerization process, influencing not only the polymeric parameters such as reaction rate, conversion and yield, but also the properties of the polymer such as molecular weight and polydispersity [19]. Several catalysts such as organic tin (e.g. $Sn(Oct)_2$) [20–29], organic aluminum (e.g. $Al(OiPr)_3$) [30] as well as organic zinc compounds [31] have been found effective for the ROP of DX. As reported by Nishida et al. [25], PDX has a ceiling temperature of 265 °C. Special precautions should be taken to process the material at the lowest temperature possible to avoid depolymerization to DX. In fact, the monomer–polymer equilibrium was described by the microreversibility model according to which all growing chains (P_n and P_{n+1}) are capable of depolymerizing until a constant monomer concentration is reached (Eq. (1)) [25]:

$$P_n + \mathrm{M} \underset{k_{dp}}{\overset{k_p}{\rightleftharpoons}} P_{n+1} \quad (1)$$

where P_n and P_{n+1} are propagating polymer chains, M is the monomer DX, and k_p and k_{dp} are the rate constants for polymerization and depolymerization respectively.

It is crucial to remove all traces of metallic catalysts in PDX before use in biomedical and pharmaceutical fields to avoid any adverse biological reactions. Metallic catalyst residues may be removed using solvent extraction [30]. This step is costly and has prompted researchers to try enzymatic polymerization of DX. Enzymatic activity is influenced by temperature, origin of enzyme and the reaction media [32]. Nishida et al. [33] reported on the successful enzymatic polymerization of DX using 5 wt% immobilized lipase at 100 °C for 15 h. However, the rate of monomer conversion is very low and hence cannot be used for large scale application. The different catalysts used for DX homopolymerization and ^{1}H NMR spectra of DX and PDX are given in Fig. 1.

Homopolymerization of racemic MeDX has been carried out using various initiator systems for instance $Sn(Oct)_2$/*n*-BuOH, $Sn(Oct)_2$ and $Al(OiPr)_3$ [18]. However DX is found to polymerize to higher conversions than MeDX irrespective of the nature of the initiator. Highest molar mass polymers with low polydispersity indices were reported with $Al(OiPr)_3$ in the temperature range 40–60 °C. Prolonged polymerization times led to a decrease in molar masses and a broadening of molar mass distribution, due probably to increased depolymerization and side reactions. The different catalysts used for MeDX homopolymerization and ^{1}H NMR spectra of MeDX and poly(methyl dioxanone) (PMeDX) are given in Fig. 2.

PDX is a semi-crystalline polymer with the glass transition temperature of about −10 °C and melting temperature of around 110 °C. PMeDX is amorphous and is soluble in tetrahydrofuran