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Review

Polyester micelles for drug delivery and cancer theranostics: Current achievements, progresses and future perspectives

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ABSTRACT

The development of tumor-targeting nanocarriers is critical important for effective treatment. The synthetic polyesters have demonstrated high potential for developing nanocarriers for cancer theranostics. Especially, the biocompatible and biodegradable polyester micelles have held great promise for cancer therapy and diagnosis, while some candidates have been translated into clinical applications or under clinical trial. In this review, we have provided the state-of-the-art of polyester micelles for drug delivery and cancer theranostics. In addition, we have summarized several major types of polyesters used in the biomedical fields, the current clinical achievements of polyester micelles and recent progresses of multi-functional polyester micelles for tumor molecular imaging and therapeutic applications.

1. Introduction

The development of drug delivery systems (DDS) with polymers has attracted much attention, due to their potential advantages in materials design and acquirement, easy modification, biocompatibility and biodegradability [1]. Until now, several types of polymers, including poly (amino acid), polyesters, dextran and chitosan *etc.*, have been applied for developing DDS [2,3], demonstrating high potential for clinical applications. Among the polymers for DDS, the polyester is one class of synthetic polymers containing repetitive ester bonds in the polymer chain. Until now, several types of polyesters have been developed for biomedical applications in tissue engineering and DDS, for instance, poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and poly(ε-caprolactone) (PCL) *etc.* [4]. In recent decades, a myriad of polyester-based DDS have been developed for cancer therapy and diagnosis, by loading with different bioactive compounds or/and imaging probes [5]. Until now, several kinds of polyester-based DDS have been approved for clinical applications, for instance, Genexol-PM, Zoladex, Signifor LAR and Bydureon *etc.* Especially, the polyester-based micelles have demonstrated high performance towards clinical applications in cancer therapy due to their biocompatible and biodegradable properties [6]. Until now, one type of polyester-based polymeric micelle for treating cancer has been approved in Korea in 2007, that is, Genexol-PM. The Genexol-PM was developed by physically entrapping the anticancer drug of paclitaxel inside the micelle formed with poly(ethylene-glycol)-poly(lactic acid) (PEG-PLA). This micelle was aimed for treating breast cancer and non-small cell lung cancer. The market of Genexol-PM, as well as the clinical trials of other types of polymeric micelle-based anticancer drugs represents the milestone of polymeric nanomedicines towards clinical translation [7].

Delivering drugs to tumors for achieving therapeutic effects is an extremely sophisticated process, but the conventional drug delivery strategy is far from adequate. The polyester micelles could load different types of bioactive compounds inside the hydrophobic core, while they are generally shield with PEG to increase the biocompatibility, stability and stealth effect. The polyester micelles could extent the half-life of the bioactive compounds in blood circulation, reduce unfavorable toxicity, and most importantly, increase the dose of delivered drug in disease sites, which is also regarded as increasing the targeting ability. The polyester micelles could extravasate from the leaky blood vessels through the EPR effect to accumulate in the tumors [8], due to the impaired function of lymphatic drainage in tumors, which procedure is generally regarded as “passive targeting”. In recent decades, some targeting molecules, which could specifically interact with the receptors that highly expressed on certain cancer cells, have been decorated on the surface of polyester micelles, to increase the targeting

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ability in an active targeting way [9]. Moreover, the polyester micelles have also been designed with stimuli-responsive functions, for instance, pH- and enzyme-responsive, for controlled releasing of the cargos in tumors, to increase the specificity of drug delivery [10]. In addition, with the advancement of nanobiotechnology and molecular imaging, some probes and contrast agents have also been incorporated inside the polyester micelles for tumor diagnosis, imaging-guided therapy and theranostics [11]. Overall, the applications of polyesters for DDS have acquired many achievements, while more advances are still in progresses, although some challenges are existed ahead.

In this review, we have summarized the common used polyesters in DDS, including their synthetic routes and properties, current achievements of polyesters for drug delivery, as well as reviewed the state-of-the-art of multi-functional polyester micelles for drug delivery and cancer theranostics, including active targeting, stimuli-responsive and multi-functional platforms. In addition, we have concluded polyesters for DDS, illustrated the challenges ahead, and perspectives of polyester micelles for clinical cancer theranostics in future.

2. Polyesters: types, synthesis routes and properties

The polymer-based drug delivery and diagnostic systems have achieved great success from bench to bedside. The synthesis of polyester polymers accounts for a crucial role for developing DDS, and the polymers should be biocompatible, biodegradable, reproducible and cost-affordable. Until now, a category of polyester polymers has been developed, and the most widely applied ones are PLA, PGA, poly(lactide-*co*-glycolide) (PLGA) and PCL [12], which are generally biodegradable and hydrophobic. The degradation ways of polyesters in physiological environment are hydrolysis, oxidation and enzymatic reaction of the ester bonds [13,14]. In this section, we describe the synthetic routes and properties of the polyesters that usually used in DDS. The main synthetic routes of polyesters are polycondensation and ring-opening polymerization (Fig. 1) [15,16]. The chemical structures, properties and biomedical applications of these polyesters have been briefly summarized in Table 1.

2.1. Poly(lactide) (PLA)

The PLA is widely used in biomedical fields for drug delivery and tissue engineering, including scaffolds, bone fixator, orthopedic screws and plates due to its relatively slow degradation rate and easy processability [17–19,22–25,28]. The PLA can be synthesized through the polycondensation of lactic acid, as well as ring-opening polymerization of lactide [58]. In directly polycondensation, the reaction kinetics and removal of the byproduct water should be strictly controlled to obtain high molecular weight (M_W) polyesters. Thus, the ring-opening polymerization is commonly used to obtain PLA with different M_W and a narrow distribution of M_W at relatively mild reaction conditions [15]. In the ring opening polymerization, the Tin(II) 2-ethylhexanoate (Sn(Oct)$_2$), a FDA (U.S. Food and Drug Administration)-approved catalyst used in medical and food industries, has been used as a standard catalyst system. As the lactic acid has two optically active stereoisomers of L- and D-lactic acids, four different polymer formulations could be obtained, including the isotactic homopolymers of poly(D-lactide) (PDLA) and poly(L-lactide) (PLLA), optically inactive poly(DL-lactide) (PDLLA) with an random sequence of D and L units, and meso-PLA from the polymerization of meso-lactide [20]. Among them, the PLLA and PDLLA are the most frequently used in the biomedical field. The diversities in polymer structure, including M_W and stereochemistry, provide a broad range of physicochemical properties, such as degradation time, tensile strength and melting temperatures, to satisfy different applications [59–62]. Particularly, the advantages of using PLA stereocomplex to construct functional colloidal systems for therapeutic applications have been realized recently [63–65]. For instance, a highly tunable nanoparticle from the layer-by-layer stereocomplex self-assembly of PLLA and PDLA on a silica-coated magnetite was developed for delivering doxorubicin (DOX) to breast cancer cells [64]. The outmost coating with pH- or temperature-responsive PLA block copolymers endowed the nanoparticle could deliver drugs in a

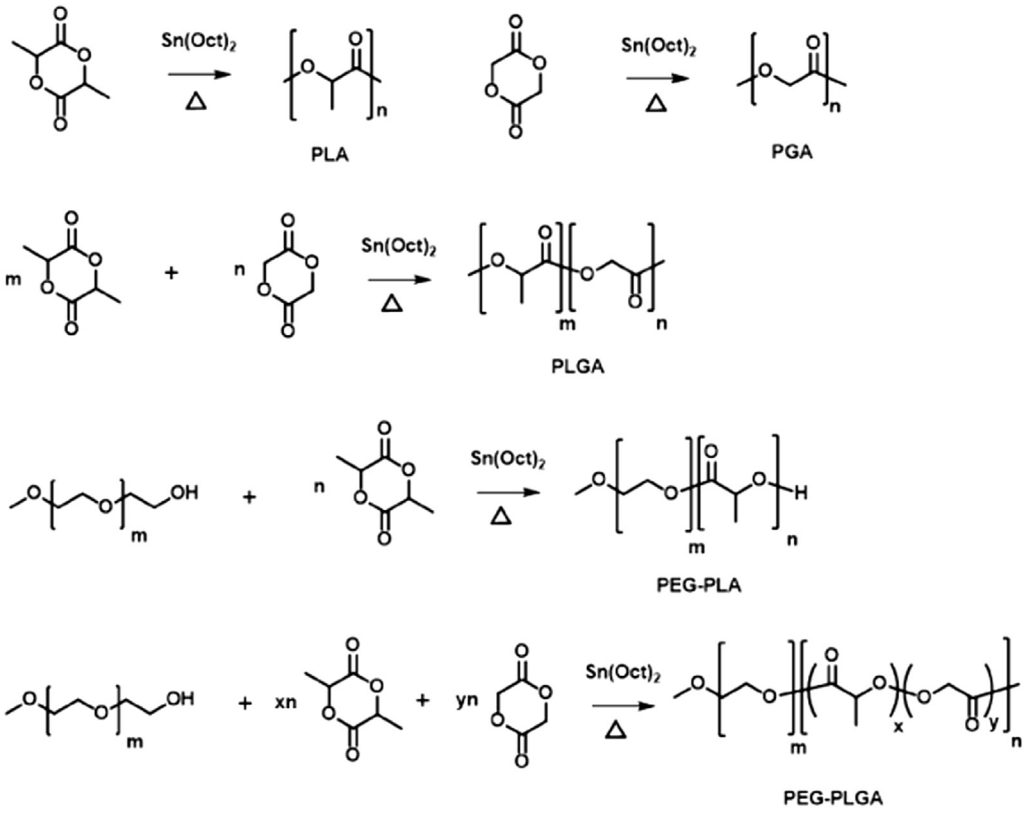

Fig. 1. Typical synthetic routes of PLA, PGA, PLGA, PEG-PLA and PEG-PLGA through ring opening polymerization.