Reactive and Functional Polymers 101 (2016) 1–8

Contents lists available at ScienceDirect

Reactive and Functional Polymers

journal homepage: www.elsevier.com/locate/react

Zidovudine insertion in tailor-made propylene and ethylene oxide copolymers

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ARTICLE INFO

Article history:
Received 8 June 2015
Received in revised form 28 January 2016
Accepted 31 January 2016
Available online 2 February 2016

Keywords:
Tailor-made polymers
Glycidyl propargyl ether
Click chemistry
Drug–polymer conjugates
Zidovudine

ABSTRACT

A synthetic strategy has been developed to create tailor-made poly(ethylene glycol) and poly(propylene glycol) copolymers functionalized with alkynyl groups that are introduced into the co-polymer chains by the addition of glycidyl propargyl ether (GPE) as co-monomer. The alkynyl-decorated copolymer obtained is used as a starter material to synthesize a drug–copolymer conjugate by copper catalyzed azide-alkyne cycloaddition (CuAAC) reaction (click reaction). This way, hydrophobic drugs can be transformed into water-soluble compounds by improving its absorbability and bioavailability by joining them to tailor-made PEG–PPG–GPE copolymers with low polydispersity and precise molecular weight. In this work, zidovudine (AZT) drug with an azide group was chosen to be attached to the polyether chain. The chemical structure of the copolymer was characterized using infrared spectroscopy, nuclear magnetic resonance, matrix-assisted laser desorption/ionization time of flight mass spectrometry and gel permeation chromatography. Finally, ^{1}H NMR spectrum confirms the successful addition of the zidovudine drug to the synthesized copolymer by the click reaction.

1. Introduction

The interest on the research field of novel therapeutic agents for the treatment of incurable pathologies such as cancer or HIV is widely spread in the scientific community. Pharmaceutical Technology (PT) is one of the most noteworthy areas. One of the most promising recently investigated routes in order to achieve this aim, is the synthesis of a drug–polymer conjugate. The idea is to join the drug molecule to a polymer that improves its stability and reduces the speed to spread into the organism [1], getting this way a long-lasting response into the organism and also reducing the amount of drug needed.

Before polymers, liposomes have been applied as carriers and it has been observed that those have high capacity to keep molecules fixed. However, their attachments can easily break or keep join incompletely and they are captured easily by endoplasmic reticulum [2]. Therefore, alternative routes using polymers are being explored.

Some of the most commonly studied polymers in the PT are polyethylene glycols (PEGs) and their derivatives. Recent studies with polyethylene and polypropylene copolymers (PEG–PPG copolymers) have demonstrated that they are able to form micelles that can improve the hydrosolubility, stability and bioavailability of drugs [3,4]. The micelle formation is due to the presence of hydrophilic and hydrophobic parts in the PEG–PPG copolymers structure, since when a critical concentration is reached (CMC) the copolymer assembles over itself forming a core–shell structure with the hydrophobic part inside (core) and the hydrophilic one outside. This way, water insoluble compounds placed in the micelle core can be easily solubilized in aqueous media [4]. The micelle formation occurs when the copolymer concentration reaches a certain concentration called the critical micelle concentration (CMC) and at a micellar temperature (CMT). Varying the EO/PO ratio and the molecular weight of these copolymers, the hydrophilicity, stability and the CMC and the CMT can be controlled; being this kind of copolymer as the most widely investigated for the micelle formation in biomedical applications [3].

PEG–PPG copolymers are synthesized by sequential polymerization of PO and EO monomers in the presence of an alkaline catalyst, such as potassium hydroxide [5,6] and also a starter of the polymerization that could be ethylene glycol, water or glycerol [7–11]. PEG–PPG copolymer could be tailored; with the desired number of OE, OP and GPE molecules and introducing the GPE in the middle of the chains, which enhances and increases the possibility of modifying this copolymer in order to get a middle-decorated PEG–PPG copolymer. Anionic polymerization usually produces polymers with a lower polydispersity index (PI) and more regiospecific than cationic polymerization which is an important characteristic for the process to add the drug to the copolymer to control the length of chains where the drug is going to be introduced [12].

Many studies have tried to improve the yield of the polymerization reaction and its selectivity towards polymers with low polydispersity index instead of the generation of dimers [13]. Besides, the molecular weight of copolymers developed for therapeutics applications must be necessarily kept in the range between 10 and 15 kDa in order to allow them to be filtered by the kidney and cleared in the urine [3], because

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http://dx.doi.org/10.1016/j.reactfunctpolym.2016.01.019
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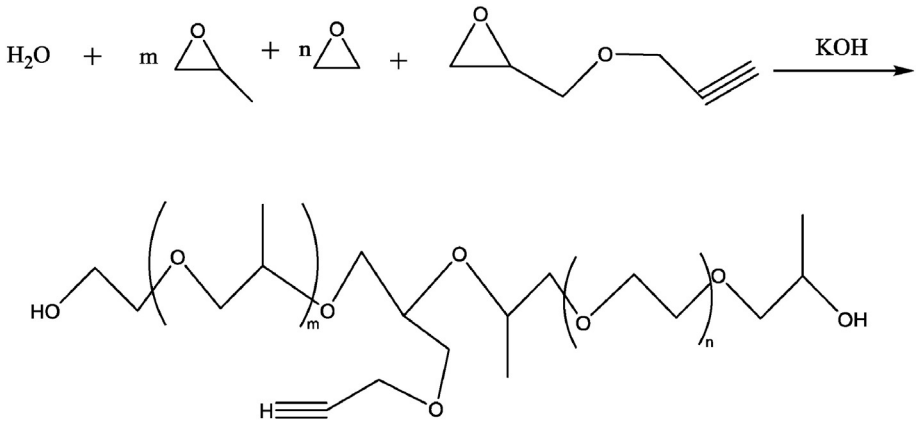
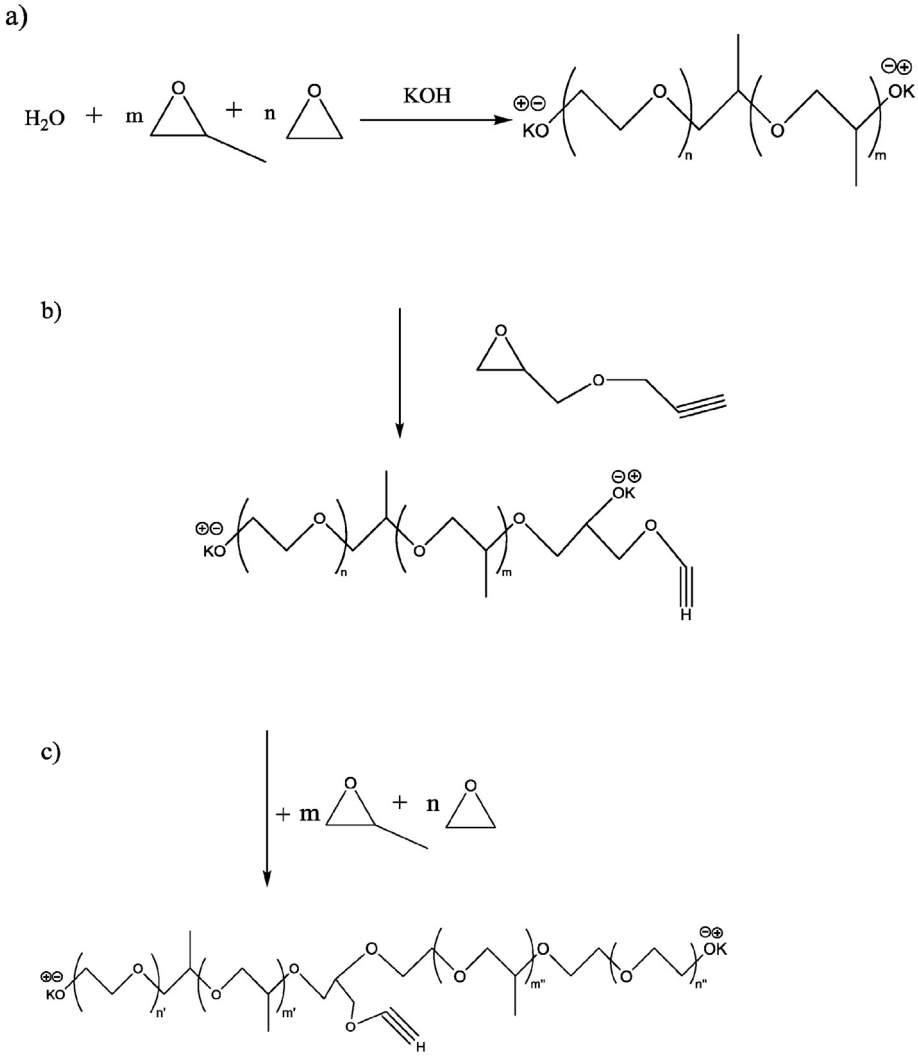


Scheme 1. Synthesis of PEG–PPG–GPE copolymer in a single step.

copolymers with higher molecular weights present worst permeability through the cell wall.

On the other hand, the success of the polymer–drug conjugate lays on the interaction between the polymer and the active drug. Depending on the specificity and the properties of functional groups present in both components, the polymer–drug interaction will have a chemical, physical or electrostatic character and the effect caused in the target cell will be different.

The addition of the drug by means of click chemistry can increase its stability due to the strength of linkage, favoring the desired long-lasting response into the organism. Some of the advantages of the click chemistry reaction are their good regioselectivity, the high-yielding, the



Scheme 2. Synthesis of PEG–PPG–GPE copolymer in three steps: a) Synthesis of PEG–PPG copolymer, b) addition of the GPE molecule to the previously synthetized copolymer and c) new addition of PO and EO to maintain the GPE in the middle of the copolymer chain.