Journal of Controlled Release 240 (2016) 191–201

Contents lists available at ScienceDirect

Journal of Controlled Release

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

PEG-*b*-PLA micelles and PLGA-*b*-PEG-*b*-PLGA sol–gels for drug delivery

Hyunah Cho [a], Jieming Gao [b], Glen S. Kwon [b,c,*]

[a] Department of Pharmaceutical and Administrative Sciences, St. Louis College of Pharmacy, 4588 Parkview Place, St. Louis, MO 63110, United States
[b] Pharmaceutical Sciences Division, School of Pharmacy, University of Wisconsin, 777 Highland Avenue, Madison, WI 53705, United States
[c] Center for Theragnosis, Biomedical Research Institute, Korea Institute of Science and Technology (KIST), Hwarangno 14-gil 5, Seongbuk-gu, Seoul 136-791, Republic of Korea

ARTICLE INFO

Article history:
Received 28 August 2015
Received in revised form 7 December 2015
Accepted 10 December 2015
Available online 15 December 2015

Keywords:
Block copolymer
Controlled release
Drug combination
Drug solubilization
Hydrogels
Polymeric micelles
Prodrugs

ABSTRACT

Poly(ethylene glycol)-*block*-poly(D,L-lactic acid) (PEG-*b*-PLA) micelles and poly(D,L-lactic-*co*-glycolic acid)-*block*-polyethylene glycol)-*block*-poly(D,L-lactic-*co*-glycolic acid) (PLGA-*b*-PEG-*b*-PLGA) sol–gels have been extensively researched for systemic and localized drug delivery applications, respectively, and they have both progressed into humans for paclitaxel, an important yet poorly water-soluble chemotherapeutic agent. In this review article, preclinical and clinical research on PEG-*b*-PLA micelles and PLGA-*b*-PEG-*b*-PLGA sol–gels that has focused on paclitaxel will be updated, and recent research on other poorly water-soluble anticancer agents and delivery of drug combinations (i.e. multi-drug delivery) that seeks synergistic anticancer efficacy will be summarized. PEG-*b*-PLA micelles are a first-generation platform for the systemic multi-delivery of poorly water soluble anticancer agents. PLGA-*b*-PEG-*b*-PLGA sol–gels are a first-generation platform for the localized multi-drug delivery of water-soluble and/or poorly water-soluble anticancer agents. In summary, PEG-*b*-PLA micelles and PLGA-*b*-PEG-*b*-PLGA sol–gels may safely enable pre-clinical evaluation and clinical translation of poorly water-soluble anticancer agents, especially for promising, rapidly emerging anticancer combinations.

1. Introduction

Anticancer drug combination is commonplace in cancer treatment, and the pace of research on novel drug combinations will likely grow moving from chemotherapy combinations towards more rational drug combinations of chemotherapy and so-called targeted agents, targeted agent combinations, and even combinations that involve compelling anticancer immunotherapies [1,2]. While drug combinations are changing, primary goals remain the same: Synergy, non-overlapping toxicity, and overcoming drug resistance. Drug combinations require formidable preclinical testing, validation and prioritization prior to clinical trials [3]. The Food and Drug Administration (FDA) in the USA has recognized the significance of emerging and innovative anticancer combinations, and it has drafted a guidance on the development of two or more novel anticancer agents in a single development program, termed co-development [4].

While target-centric research has received a lot of attention in anticancer drug development, opportunities in the delivery of drug combinations, i.e. multi-drug delivery, have been largely overlooked and not appreciated in the scope of gaining synergy. Are there safe and simple ways to deliver poorly water-soluble anticancer drug combinations? Do drug combinations reach solid tumors at effective levels without widespread non-target distribution? Can we take advantage of the enhanced permeability and retention (EPR) effect for drug combinations, and in this context is tumor drug ratio important? While often not appreciated, novel concepts and drug delivery systems are emerging that satisfy requirements in solubility, safety and scale-up and may permit advances in drug delivery that move beyond the EPR effect, e.g. tumor priming, ratiometric dosing [5–7].

Bock copolymers based on poly(ethylene glycol (PEG) and poly(α-hydroxy acid) such as poly(D,L-lactic acid) (PLA) and poly(lactic-co-glycolic acid) (PLGA) are being studied for drug delivery, owing to their biocompatibility, controlled biodegradability of poly(α-hydroxy acid), relative ease of polymer synthesis and preparation of a variety of nano- to macro-scale forms and sizes: Polymeric micelles, nanoparticles, polymersomes, and sol–gels [8–11]. Block copolymers based on PEG and poly(α-hydroxy acid) have been studied for the delivery of hydrophobic and hydrophilic drugs; in the former case, poorly water-soluble paclitaxel, has been widely studied, and there is an approved product based on poly(ethylene glycol)-*block*-poly(D,L-lactic acid) (PEG-*b*-PLA) micelles in Asia (Fig. 1). In the latter case, feasibility of controlled release of insulin from a poly(D,L-lactic-*co*-glycolic acid)-*block*-polyethylene glycol)-*block*-poly(D,L-lactic-*co*-glycolic acid) (PLGA-*b*-PEG-*b*-PLGA) sol–gel has been established (Fig. 1). Block copolymers based on PEG and poly(α-hydroxy acid) have been studied for systemic and local drug delivery, and with the advent of the field of nanomedicine, they have played a central role in drug targeting efforts. Local or regional drug delivery has increasingly gained attention, and block copolymers based on PEG and poly(α-hydroxy acid) have potential for localized cancers, such as brain, ovarian and esophageal cancers. Block copolymers based on PEG and poly(α-hydroxy acid) may be used for the delivery of drug combinations (i.e. multi-

* Corresponding author at: Pharmaceutical Sciences Division, School of Pharmacy, University of Wisconsin, 777 Highland Avenue, Madison, WI 53705, United States.
E-mail address: gskwon@pharmacy.wisc.edu (G.S. Kwon).

http://dx.doi.org/10.1016/j.jconrel.2015.12.015
0168-3659/

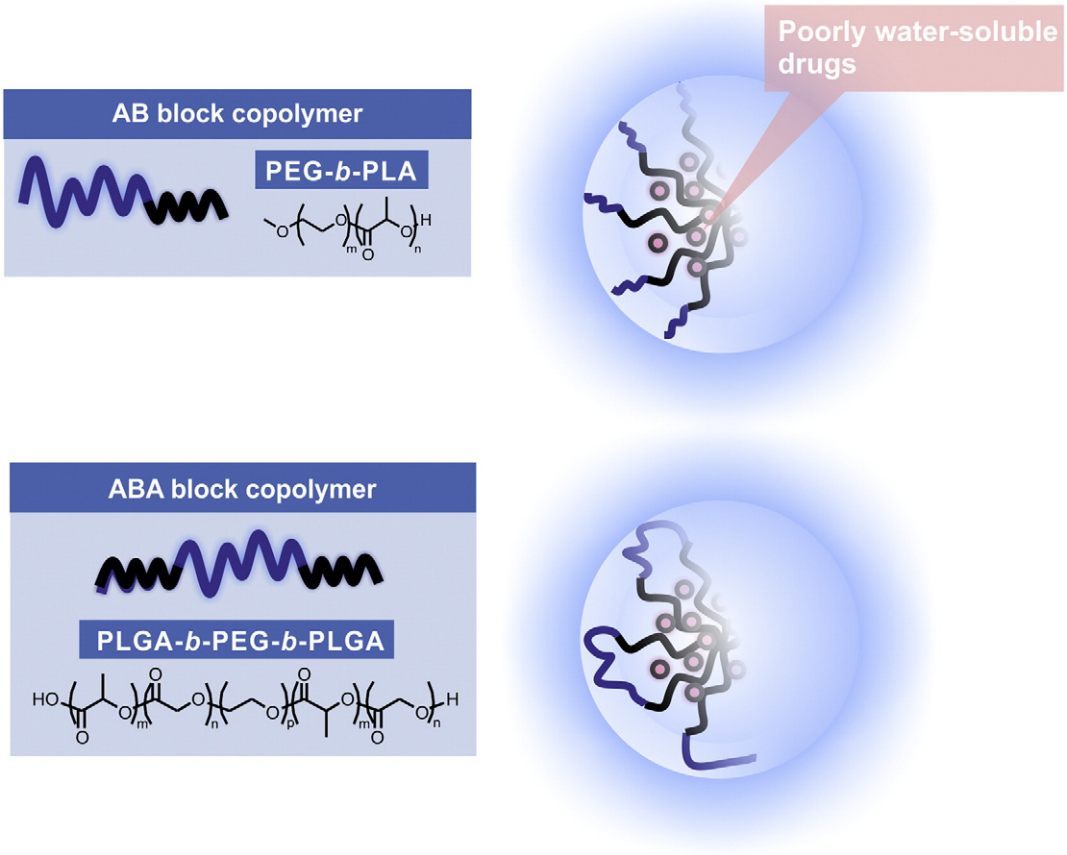

Fig. 1. PEG-*b*-PLA and PLGA-*b*-PEG-*b*-PLGA block copolymers for drug delivery. Both assemble into micelles for drug solubilization. The latter micelles exist with PEG loops in the shell region, and they form a controlled release gel at above the sol–gel transition temperature.

drug delivery), and recent efforts in multi-drug delivery have been the subject of compelling review articles that summarize synthetic strategies, physicochemical characterization, controlled release mechanisms and pre-clinical and clinical studies [12–15].

The aim of this review article is to summarize recent progress on PEG-*b*-PLA micelles and PLGA-*b*-PEG-*b*-PLGA sol–gels for systemic and local drug delivery, respectively, and describe efforts in multi-drug delivery. PEG-*b*-PLA micelles and PLGA-*b*-PEG-*b*-PLGA sol–gels have been tested extensively in humans and have proven safety profiles and proven to be amendable to scale-up for human clinical trials. Because PEG-*b*-PLA micelles and PLGA-*b*-PEG-*b*-PLGA sol–gels have been reviewed nicely elsewhere [8,11], emphasis will be placed on newly tested anticancer agents and clinical developments, especially for paclitaxel. In addition, recent research has revealed that PEG-*b*-PLA micelles and PLGA-*b*-PEG-*b*-PLGA sol–gels have a unique capacity for multiple poorly water-soluble anticancer agents, offering a new perspective on delivery of drug combinations. This work will be discussed in the context of drug delivery research that seeks to seamlessly and safely translate novel drug combinations into animal models and ultimately into humans. Lastly, research efforts on PEG-*b*-PLA micelles and PLGA-*b*-PEG-*b*-PLGA sol–gels that pursue novel drug delivery strategies will be discussed with the goal of showing the feasibility of drug delivery beyond the scope of current paradigms in drug solubilization and local sustained release effects.

2. PEG-*b*-PLA micelles

Many review articles over the years have described polymeric micelles for drug delivery and have charted progress into clinical trials [8,14,15–20]. Most block copolymers have a hydrophilic block that is PEG and hydrophobic blocks are commonly poly(propylene glycol), poly(α-amino acid) or poly(α-hydroxy acid), providing structural variation for chemical (prodrug) and physical drug loading strategies. The first description of PEG-*b*-PLA dispersions can be found in a European patent application by Churchill and Huchinson in 1985 [21]. Interestingly, it portends ensuing research on PEG-*b*-PLA micelles for drug delivery of poorly water drugs: In this patent application, they described block copolymers that possess a hydrophobic, biodegradable block and a hydrophilic block that may or may not be biodegradable and that are rapidly self-dispersible in water, which is indicative of polymeric micelles. In example 1, they described an AB block copolymer that has a PEG at 5900 g/mol and a PLA block at 75% by weight, and it was dissolved in glacial acetic acid and stirred vigorously with excess distilled water to produce an extremely fine dispersion. It could be freeze-dried and subsequently reconstituted with water to form a very fine dispersion. In example 6, it was shown that PEG-*b*-PLA dispersions (50% PLA by weight) could solubilize a poorly water-soluble antiestrogen, ICU 189150, which is suitable for injection. In claim 9, they described a process for the manufacture of a frozen, stable aqueous dispersion of a copolymer and a water-insoluble drug, characterized by dissolving the drug and the self-dispersible copolymer in a minimum amount of a water-miscible organic solvent, slowly adding an excess of water to the vigorously agitated solution to produce a fine, stable dispersion and then freezing the dispersion. In summary, results in this European patent application were the first to show drug solubilization by PEG-*b*-PLA dispersions as an alternative strategy for injection, moving beyond the scope of pH adjustment, cosolvents, and surfactants such as Cremophor EL.

2.1. PEG-b-PLA micelles for drug solubilization

Table 1 summarizes anticancer agents that have been incorporated in PEG-*b*-PLA micelles and fulfill the requirement of drug solubilization