Advanced Drug Delivery Reviews 115 (2017) 155–170

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

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

Near-infrared light-activatable polymeric nanoformulations for combined therapy and imaging of cancer☆

Xiuli Yue [b], Qiang Zhang [a], Zhifei Dai [a,*]

[a] Beijing Key Laboratory of Molecular Pharmaceutics and New Drug Delivery Systems, College of Engineering, College of Pharmaceutics, Peking University, Beijing 100871, China
[b] School of Municipal and Environmental Engineering, Harbin Institute of Technology, Harbin 150080, China

ARTICLE INFO

Article history:
Received 6 January 2017
Received in revised form 16 March 2017
Accepted 19 April 2017
Available online 25 April 2017

Keywords:
Near infrared polymer
Photothermal therapy
Cancer theranostics
Cancer imaging
Triggered drug release
Combined cancer therapy

ABSTRACT

Near infrared (NIR) light allows deep tissue penetration and high spatial resolution due to the reduced scattering of long-wavelength photons. NIR light-activatable polymer nanoparticles are widely exploited for enhanced cancer imaging (diagnosis) and therapy owing to their superior photostability, photothermal conversion efficiency (or high emission rate), and minimal toxicity to cells and tissues. This review surveys the most recent advances in the synthesis of different NIR-absorbing and emissive polymer nanoformulations, and their applications for cancer imaging, photothermal therapy, theranostics and combination therapy by delivering multiple small molecule chemotherapeutics. Photo-responsive drug delivery systems for NIR light-triggered drug release are also discussed with particular emphasis on their molecular designs and formulations as well as photo-reaction mechanisms. Finally, outlook and challenges are presented regarding potential clinical applications of NIR light-activatable nanoformulations.

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Nanoformulations for combination or cascade anticancer".

* Corresponding author.
E-mail address: zhifei.dai@pku.edu.cn (Z. Dai).
URL: http://bme.pku.edu.cn/~daizhifei/ (Z. Dai).

http://dx.doi.org/10.1016/j.addr.2017.04.007
0169-409X/

1. Introduction

Nanoparticle (NP) anticancer drug delivery promises a disruptive technology to improve cancer therapeutic efficacies and reduce side effects. Unfortunately, a majority of monotherapy nanomedicines have failed to obtain better chemotherapeutic outcomes than conventional chemotherapy in human clinical trials in spite of promising preclinical efficacy results. To address this issue, recent efforts have been devoted to designing combination nanomedicines rationally to accommodate the multiple drugs or therapeutic modalities with temporally controlled release to afford synergistic therapeutic effect for conquering the tumor heterogeneity and drug resistance issues [1].

Near infrared (NIR) light takes advantage for the use of phototherapy and optical imaging within deep tissues due to the minimal scattering or autofluorescence of biological species in the NIR spectrum in comparison with UV/visible light [2,3]. NIR nanomaterials have emerged as a promising effective platform that integrates different aspects of chemistry, biology, bioinformatics, medical physics and various other fields to form a joint solution to various problems in cancer diagnosis and therapy today [4,5]. Especially, NIR polymers have attracted intensive research interests in various biomedical applications since they have not only unique optical properties similar to those of metals and inorganic semiconductors, but also intriguing properties similar to those of common polymers, such as ease of synthesis, good processability and impressing biocompatibility [6]. Nanoparticles based on various NIR-absorbing polymers, such as polypyrrole (PPy) [6] and polyaniline (PANi) [7], have been developed as promising contrast agents for a number of imaging modalities [8] and photothermal agents for cancer photothermal therapy (PTT) [6] due to their excellent photostability and high-photothermal conversion efficiency. In addition, semiconducting polymer fluorescence NPs (Pdots) have emerged very recently as a novel type of highly fluorescent probes which own extraordinary fluorescence brightness, superior photostability, high emission rates, and minimal toxicity to cells and tissues [9]. Pdot-based NIR fluorescent probes provide remarkable advantages over conventional small fluorophores since most NIR fluorescent dyes are subjected to poor solubility in aqueous solutions, fast photobleaching, low fluorescence brightness, and small Stokes shift [10]. In addition, multiple types of therapeutic molecules and/or imaging agents can be simultaneously co-loaded into the NIR polymer NPs for cancer combination therapy and theranostics [11].

Recently, NIR light-responsive drug delivery systems with spatiotemporal control and on-demand drug release have been actively explored to overcome inherent challenges in conventional drug delivery systems due to differentially enhanced drug accumulation at targeted lesions, drastically reduced systemic toxicity, and potential avoidance of under- or overdosing [12–15]. Compared with other types of external physical stimuli used to trigger, control, and/or enhance localized cancer therapy, such as magnetic field [16,17], enzyme [18], pH [19], ultrasound [20,21], and heat [22,23], NIR light is of special importance owing to its convenient manipulation, capability to be locally focused on a specific site, and minimal absorption by skin and tissues, blood and water to permit noninvasive propagation of reasonably deep tissues [24,25]. A variety of NIR-responsive polymers with photochromic moieties have been synthesized for the fabrication of NIR-responsive micelles. The pre-loaded drug can be released on demand by exposure to NIR light to induce the disruption and disassembly of micellar forms of drug carriers [26]. Moreover, such NIR-responsive polymers with photochromic moieties could be used to fabricate multifunctional nanomedicine capable for carrying multiple therapeutic and imaging agents for accurate diagnosis and controlled drug delivery [15].

In the current review, we summarize recent progress in designing multifunctional nanomedicine for combined therapy and imaging of cancer based on the NIR light-activatable polymers after being classified into three categories: (1) NIR absorbing polymers for the use as photothermal agents for PTT ablation of cancer cells or photoacoustic imaging owing to their high optical extinction coefficients in the NIR wavelength range, (2) NIR emissive polymers to be applied for NIR fluorescence imaging of cancer, (3) NIR light-responsive polymers used as drug carriers for triggered drug release via the photo-reaction of the polymer's typical photochromic moieties under NIR light exposure. We mainly focus on the molecular design and formulation of the NIR light-activatable NPs to provide fruitful insights into the design of theranostic nanomedicines for personalized cancer treatments.

2. Synthesis of NIR light-activatable polymers and relating nanoparticles

2.1. NIR absorbing polymers and relating nanoparticles

Many NIR absorbing polymers have been recently synthesized for the use as photothermal agents. Fig. 1 shows some typical chemical structures of NIR conjugated polymers, such as polypyrrole [6], polyaniline [7], poly[9,9-bis(4-(2-ethylhexyl)phenyl)fluorene-alt-*co*-6,7-bis(4-(hexyloxy)phenyl)-4,9-di(thiophen-2-yl)-thiadiazoloquinoxaline] (PFTTQ) [27], poly(3,4-ethylenedioxythiophene):poly(4-styrenesulfonate) (PEDOT:PSS) [28], poly[4,4-bis(2-ethylhexyl)-cyclopenta[2,1-b;3,4-b′]dithiophene-2,6-diyl-alt-2,1,3-benzothiodiazole-4,7-diyl] (PCPDTBT) and poly[4,4-bis(2-ethylhexyl)-cyclopenta[2,1-b;3,4-b′]dithiophene-2,6-diyl-alt-2,1,3-benzoselenadiazole-4,7-diyl] (PCPDTBSe) [29,30].

Most of the conjugated polymers are prepared by oxidative coupling monocyclic precursors [31]. PPy and its derivatives are usually synthesized from various co-monomers or substituents through the chemical oxidation method with an oxidant (e.g., $(NH_4)_2S_2O_8$, $FeCl_3$, H_2O_2) or electrochemical oxidation method by employing an oxidizing potential. PPy is formed via the cationic radical (i.e., oxidative) polymerization of pyrrole through a pseudo-polycondensation mechanism. Starting from a one electron oxidation of pyrrole monomers to radical cations, the 2, 20-bipyrroles are generated by coupling two pyrrole radical cations, followed by coupling with another radical cation [32]. This coupling process is then repeated until longer chains are obtained. In particular, the degradation and sparing (erosion) of the principal macromolecular backbone of polymeric materials can be achieved by substituting the PPy backbone with ionizable (butyric acid) or hydrolysable (butyric ester) side groups. In addition, the degradation and erosion rate can be adjusted by varying the amount of these groups. Domagala et al. synthesized a series of pyrrole homopolymers (PPyCOO-*g*-OHB) and copolymers (PPy-*co*-PyCOO)-*g*-OHB) via chemical oxidative polymerization of 1-(2-carboxyethyl)pyrrole (PyCOOH) or copolymerization of PyCOOH with pyrrole, followed by appending the OHB side chains through off-polymer anionic oligomerization of β-butyrolactone initiated with potassium salt of the 1-(2-carboxyethyl)pyrrole group (Fig. 2) [33]. The study on the structure–property relationship revealed that the plasticity and deteriorated electrical conductivity of the PPy-*g*-OHB copolymers were improved by increasing number of OHB units. The OHB length and grafting density had profound effect on the extent of the degradation and erosion process. The copolymers with short OHB