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Environmental pH-sensitive polymeric micelles for cancer diagnosis and targeted therapy

Guang Hui Gao [1], Yi Li, Doo Sung Lee *

Department of Polymer Science and Engineering, Theranostic Macromolecules Research Center, Sungkyunkwan University, Suwon, Republic of Korea

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ABSTRACT

The delivery and control over the release of hydrophobic imaging markers for cancer diagnosis or pharmaceutical agents for targeted therapy are of considerable interest. Nano-sized pH-sensitive polymeric micelles that rely on the enhanced permeability and retention (EPR) of vasculature and the low-pH microenvironment in cancer tissue are emerging as stimuli-responsive targeted therapies that can simultaneously release diagnostic and therapeutic agents into a cancerous region. This review focuses on the developments of pH-sensitive polymeric micelles and their biomedical applications in cancer diagnosis and targeted therapy.

1. Introduction

Nanotechnology brings certain dramatic advantages to biomedical applications [1,2]. For example, nano-sized polymeric micelles may be utilized as carriers for the delivery and controlled release of imaging agents and drugs in the context of cancer diagnosis and targeted therapy [3,4]. Pharmaceutical carriers target cancer tissues based on local stimuli [5].

Nano-sized polymeric micelles can deliver hydrophobic imaging agents or drugs that accumulate in cancer tissue via the enhanced permeability and retention (EPR) effect. The EPR effect is observed in pathological vasculature structures, which display enhanced leakiness, and not in the vessels of normal tissues [6,7]. The pore size in a cancer blood vessel ranges from 200 nm to 780 nm. The EPR effects that arise from the large pore size permit the passage of nano-sized polymeric micelles that passively target and accumulate in a tumor due to the cutoff size in the leaky vasculature. The extracellular pH (pH_e) in normal tissue and blood is usually held constant at pH 7.2–7.4; however, the mean pH_e in various solid tumors is usually below 7.0. The low tumor pH primarily results from a high glycolysis rate, which can produce lactic acid (or other types of acids) under both aerobic and anaerobic conditions [8,9]. The low pH_e benefits tumor cells and promotes invasive cell growth. The low pH in the tumor extracellular matrix provides a tissue-specific stimulus that may be exploited for targeting applications.

A number of hydrophobic imaging markers and pharmaceutical agents (e.g. Fe_3O_4, doxorubicin, or paclitaxel) have emerged in potential clinical applications in the field of cancer diagnosis and therapy [10–12]. However, the delivery of such diagnostic and therapeutic agents has suffered from several challenges, including poor absorption, low biocompatibility, a short circulation time in the blood, and a high local toxicity in normal vessels or tissues. Therefore, amphiphilic diblock copolymers that self-assemble to form core-shell structured micelles are potential candidate carrier vehicles for poorly water-soluble drugs and diagnostic agents [13]. Water-insoluble drugs or diagnostic agents can be encapsulated into the hydrophobic cores or the outer hydrophilic shells of micelles to form a stable dispersion in aqueous media. Polymeric micelles should display four principal qualities: (1) they should be in nano-scaled sizes (50–200 nm) upon encapsulation of the drug or imaging agent; (2) they should display prolonged circulation times in the blood after intravenous injection; (3) they should carry their pharmaceutical cargo to the diseased tissue under the EPR effects; and (4) they should respond to the local pH at cancer sites to control the release of their pharmaceutical cargo (Fig. 1). As a result, polymeric micelles may be designed to display tunable pH sensitivity and controlled release by introducing ionizable amino groups into their backbones. pH-sensitive polymeric micelles can be designed to carry, deliver, and control the release of hydrophobic agents in cancer tissue by relying on the EPR effects and the low pH in the vicinity of a cancer tissue.

* Corresponding author at: Department of Polymer Science and Engineering, Theranostic Macromolecules Research Center, Sungkyunkwan University, Suwon 440-746, Republic of Korea. Tel.: +82 31 290 7282; fax: +82 31 292 8790.
E-mail address: dslee@skku.edu (D.S. Lee).
[1] Dr. Guang Hui Gao is presently a Professor in the Engineering Research Center of Synthetic Resin and Special Fiber, Ministry of Education, Changchun University of Technology, China.

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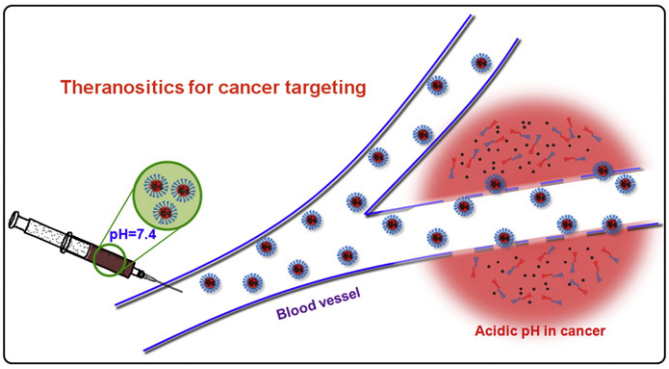

Fig. 1. Scheme of enhanced permeability and retention (EPR) effect and acidic controlled release in the cancer area.

2. pH-sensitive polymeric micelles

The pH-sensitive polymers consist of ionizable groups that can accept or donate protons in response to an environmental pH change [14–17]. As the environmental pH values change, the ionization of a polymer comprising weakly ionizable groups can be dramatically altered at the relevant pK_a. The rapid shift in ionization can alter the hydrodynamic diameter and molecular state of the polymer chains. The transition from a collapsed to an expanded state can be described in terms of the osmotic pressure released by the mobile counterions that solvate and neutralize the newly formed charges. Two types of pH-sensitive polyelectrolyte may be developed: anionic and cationic polymers.

2.1. Anionic polymers

Anionic polymers containing carboxylic acid groups are the most commonly used as pH-sensitive polymers. Such polymers include poly(acrylic acid) (PAAc) and poly(methacrylic acid) (PMAAc), as shown in Fig. 2(a,b). The pendant carboxylic acid groups of such polymers are protonated at low pH, yielding neutral molecules that are relatively hydrophobic. At neutral or high pH, the molecules can release protons and become hydrophilic. PMAAc displays a relatively abrupt phase transition and a compact conformation in comparison to PAAc prior to the critical transition because the methyl groups in PMAAc induce stronger hydrophobic interactions that promote aggregation.

Another type of pH-sensitive anionic polymers are those containing sulfonamide groups [18], the pK_a of which can range from pH 3 to 11, depending on the pendant substituents on the sulfonamide groups (Fig. 2(c)). The acidic protons of sulfonamide groups are readily ionized upon an increase in pH. The behaviors of these polymers can be controlled over a narrow pH range and display a higher level of sensitivity compared to conventional carboxylic acid-based polymers.

The most common synthetic anionic polypeptide used in polymeric micelles is poly(glutamic acid) [19], which consists of amino acids with carboxylic acid group side chains (Fig. 2(d)). This polymer undergoes a pH-responsive hydrophilic–hydrophobic phase transition via a helix-coil conformational change upon experiencing an environmental pH jump.

2.2. Cationic polymers

Poly(N,N′-dimethyl aminoethyl methacrylate) (PDMAEMA) is a pH-sensitive cationic polymer with ionizable tertiary amine group side chains (Fig. 3(a)). The tertiary amine can bind protons to form cationic groups under acidic pH conditions and subsequently release the protons under basic conditions. Another cationic polymer, poly(4-vinylpyridine) (PVP), undergoes a phase transition upon deprotonation of the pyridine groups at pH 5 (Fig. 3(b)).

Poly(histidine) forms an artificial cationic polypeptide [20], and has been extensively investigated for use in pharmaceutical carrier formulations because it is biocompatible and appropriately pH-sensitive. Poly(histidine) contains imidazole pendant groups that are neutral at high pH and undergo protonation at pH 5–6.5 (Fig. 3(c)).

A pH-sensitive biodegradable cationic polymer, poly(β-amino ester) (PAE), which includes tertiary amine groups (Fig. 3(d)), has been extensively studied in recent years [21]. PAE may be synthesized by using bis(secondary amines) or primary amines and bis(acrylate ester) groups. This polymer undergoes a hydrophobic–hydrophilic phase transition upon a decrease in pH from basic to acidic. The polymer rapidly solubilizes at pH values below the pK_a. These polymers are noncytotoxic and degrade into nontoxic small molecule byproducts.

2.3. Acid-labile polymers

Acid-labile polymers have received considerable attention in the field of pH-sensitive drug delivery to cancer tissue. These polymers have acid-labile bonds that are generally stable at pH 7.4 but are

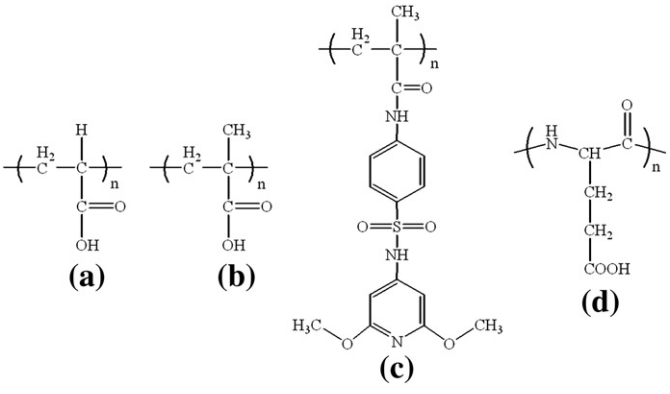

Fig. 2. Molecular formula of representative pH-sensitive anionic polymers: (a) poly(acrylic acid) (PAAc); (b) poly(methacrylic acid) (PMAAc); (c) polymer containing sulfonamide groups; and (d) poly(glutamic acid).

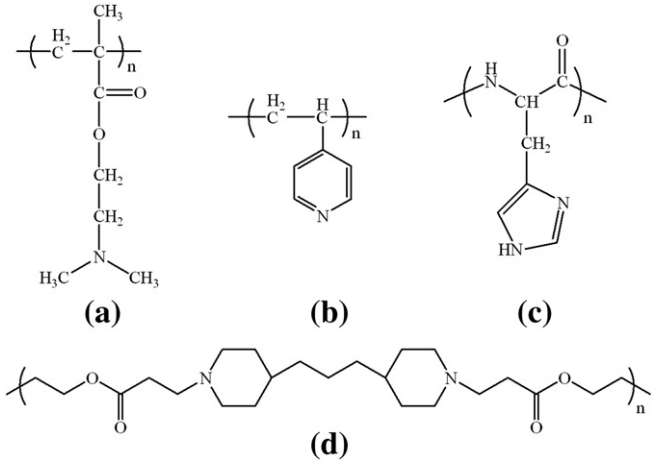

Fig. 3. Molecular formula of representative pH-sensitive cationic polymers: (a) poly(N, N′-dimethyl aminoethyl methacrylate) (PDMAEMA); (b) poly(4-vinylpyridine) (PVP); (c) poly(histidine); and (d) poly(β-amino ester).