pH-Triggered Targeting Polymeric Nanocarriers: Theranostic Applications

Doo Sung Lee
Theranostic Macromolecules Research Center (ERC), School of Chemical Engineering,
Sungkyunkwan University, Korea
Phone +82-31-290-7282, Fax +82-31-292-8790, E-Mail: dslee@skku.edu

Abstract

In pharmaceutical field, small molecules drugs face a lot of challenges such as non-specific absorption, poor pharmacokinetics, and off-target accumulation; whereas the bio-macromolecular medicines are obstructed due to quick degradation, invasive nature, and non-targeting uptakes. To overcome those obstacles, drug delivery system (DDS) has gained huge interests as an emerging technique for reducing systemic drug toxicity and increasing the therapeutic efficacy. In recent years, numerous of smart artificial drug delivery systems (DDS), which can triggered-release the payload under changes in environmental factors (e.g. pH, temperature, enzyme, etc.) to achieve the ultimate goals of drug delivery system, have been evolved and developed [1]. Among those DDSs, based on the pH difference between pathological tissues and normal tissues, pH-responsive polymeric DDS can be administered directly to the blood and deliver the majority of the drug to the intended pH-gradients. Various polymeric materials have been employed to prepare nanosized pH-sensitive DDS with high potency for clinical applications [2, 3].

For last decade, our researches focus on developing the pH-triggered targeting polymeric nanocarriers, which are based on titratable-polymers/copolymers for theranostic applications. Aiming to the acidic pathological tissues like extracellular tumor tissues and ischemic stroke area, our nanocarriers can deliver and release the theranostic agents to the targeted acidic zones after a stable journey in blood circulation. Generally, our pH-sensitive amphiphilic polymers/copolymers can be prepared from hydrophilic polyethylene glycol (PEG) and pH-sensitive hydrophobic blocks as sulfonamide-related polymer, poly(β-amino ester) (PAE), and polypeptide. Firstly, Sulfonamide monomers, which have pKa 6.1-7.4 are selected to offer the titratable properties for anionic copolymers that display rapid association-dissociation transition at pH above 7.4. At pH higher than 7.4, soluble state of sulfonamide-related polymers allows to entrap pharmaceutic molecules due to the formation of micellar particles when pH drops to lower than 7.4. Secondly, PAE a well-known biodegradable cationic polymer, is mainly synthesized via Michael addition polymerization between bis(secondary amines) or primary amine monomers and bis(acrylate ester) monomers. The ionizable tertiary amine groups enable the resultant PAE undergoes a hydrophobic-hydrophilic phase transition upon pH change from basic to acidic along with the particle assembly-disassembly progression. Lastly, by using ring-opening polymerization of N-carboxyanhydride monomers to achieve polypeptide with highly feasible modification in which tertiary amine groups or other functional groups can be chemically incorporated to the peptide backbone via aminolysis process. These pH-sensitive polypeptide polymers perform dissolution and self-assembly state in acidic environment and physiological condition, respectively. Using those amphiphilic copolymers, assorted polymeric micelles and polymersomes have been erected for delivering therapeutic molecules and imaging agents, which possess high stability with long-term blood circulation, quick structure collapse inducing rapid payload release at targeted pH zones. Various hydrophobic anticancer drugs (e.g. DOX, PTX, TAXOL, CPT, etc.) and therapeutic macromolecules (e.g. DNA, SDF-1α, etc.) have been physically encapsulated to evaluate applicability of our DDS through a series of *in vitro* and *in vivo* experiments. Alternatively, inorganic imaging agents such as iron oxides Fe_3O_4 nanoparticles, quantum dots (QDs) which are usually highly toxicity due to the hazardous surfactants, can be loaded and delivered by our pH-sensitive nanocarriers. PAE or polypeptide, which contain hydrophilic shell PEG and specific functional groups can anchor on the nanoparticle's surfaces to achieve high particle loading efficiency, protect the particle from non-specific adsorption, and diminish the systemic cytotoxicity. Thereafter, at targeting tumoral extracellular or ischemia stroke environments, Fe_3O_4 or QDs can be gradually accumulated, which are able visualized by magnetic resonance imaging (MRI) and in vivo imaging system (IVIS). Those positive results of therapeutic efficiency as well as high intensive diagnostic demonstrated the clinical potential of our propose concepts. Further details about our achievements shall be discussed in our delivered presentation.

Keywords: pH, targeting, nanocarriers, cancer theranostic.

Reference

[1] D. Brambilla, P. Luciani, and J. C. Leroux. *J. Control. Release*, 2014, 190, 9-14
[2] W. Gao, J. M. Chan, and O. C. Farokhzad. *Mol. Phar.*, 2010, 7, 1913-1920
[3] G. H. Gao, Y. Li and D. S. Lee. *J. Control. Release*, 2013, 169, 180-184