Journal of Controlled Release 130 (2008) 121–128

Contents lists available at ScienceDirect

Journal of Controlled Release

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

Multi-functional nanocarriers for targeted delivery of drugs and genes

Lara Jabr-Milane [a], Lilian van Vlerken [b], Harikrishna Devalapally [c], Dinesh Shenoy [d], Sushma Komareddy [e], Mayank Bhavsar [f], Mansoor Amiji [a,*]

[a] Department of Pharmaceutical Sciences, School of Pharmacy, Northeastern University, Boston, MA 02115, United States
[b] CytImmune, Inc., Rockville, MD 20850, United States
[c] Nanotechnology Characterization Laboratories, National Cancer Institute, Frederick, MD 21702, United States
[d] Novavax, Inc., Rockville, MD 20850, United States
[e] Novartis Institute of Biomedical Research, Cambridge, MA 02139,, United States
[f] ArQule, Inc., Woburn, MA 01801, United States

ARTICLE INFO

Article history:
Received 22 March 2008
Accepted 16 April 2008
Available online 29 April 2008

Keywords:
Multi-functional nanocarriers
Stimuli-responsive
Drug delivery
Gene delivery
Biological barriers
Multi-drug resistance

ABSTRACT

In this review article, we describe the different nano-platforms developed in our laboratory at Northeastern University in Boston, MA for the targeted delivery of drugs and genes. Special emphasis is placed on nano-platforms that offer opportunities for multi-functionalization to allow for targeted stimuli-responsive and/or simultaneous strategic delivery of multiple drugs, genes, as well as the combination of therapeutic systems with image contrast enhancers. Polymeric and lipid-based nanocarriers can provide versatile platforms for the delivery of multiple pharmacological agents, specifically to enhance therapeutic effect and overcome drug resistance in cancer. In addition, polymeric nanoparticles and nanoparticles-in-microsphere oral system (NiMOS) are useful for systemic and oral gene therapy, respectively.

1. Introduction

Every biological level of organization presents a unique set of barriers to the delivery of therapeutic agents. These barriers include target specific localization, enhanced clearance, selectivity and permeability of biological membranes, metabolizing enzymes, and endosomal/lysosomal degradation. Considering these barriers, the traditional focus of drug delivery systems has been the optimization of pharmacokinetics and biodistribution [1]. As biological and drug delivery research has progressed, comprehensive strategies such as the use of multi-functional delivery systems have emerged. Through a synergistic effect, multi-functional carriers are capable of overcoming distinct physiological barriers and delivering therapeutic payload(s) and/or image contrast enhancement agents to target sites in the body. Due to the unique properties of nano-scale matter, the diversity of available materials, and infinite design schemes, nanocarriers have emerged as ideal platforms for achieving multi-functionalization [2]. Over the last eight years, our laboratory at Northeastern University has developed an array of multi-functional nanocarriers for the delivery of genes, drugs, and imaging modalities. These flexible platforms consist of polymeric and lipid systems that combine different modalities and stimuli-responsive release properties.

2. Multi-functional nanocarriers

The diagnostic and/or therapeutic objectives of a multi-functional nanocarrier system dictate the design of the formulation. A review of the literature obviates that there are many different types of nanocarrier formulations for the diagnosis, imaging, and treatment of a wide spectrum of diseases. These multi-functional carriers share three main design components: platform (core) material, encapsulated payload/biologically active agents, and targeting/surface properties (Fig. 1). Nanocarrier platforms can be categorized as organic-based, inorganic-based or a hybrid combination of the aforementioned. Organic nano-platforms include polymeric nanocarriers, lipid-based nanocarriers (e.g., liposomes and nanoemulsions), dendrimers, and carbon-based nanocarriers (e.g., fullerenes and carbon nanotubes). Inorganic nano-platforms include metallic nanostructures, silica nanoparticles, and quantum dots. An example of a hybrid platform is colloidal gold encapsulated in liposomes or superparamagnetic iron oxide particles encapsulated in polymeric nanoparticles. Selection of the core material is highly dependent on the properties of the biologically active agents. Inherent and dynamic properties of the agents such as therapeutic index, lipophilicity, charge, and size should be considered.

As the arsenal of available biologically active agents continues to expand, there are innumerable therapeutic combinations. When combining therapeutic agents with each other, with an imaging/diagnostic

* Corresponding author. Tel.: +1 617 373 3137; fax: +1 617 373 8886.
E-mail address: m.amiji@neu.edu (M. Amiji).

0168-3659/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.jconrel.2008.04.016

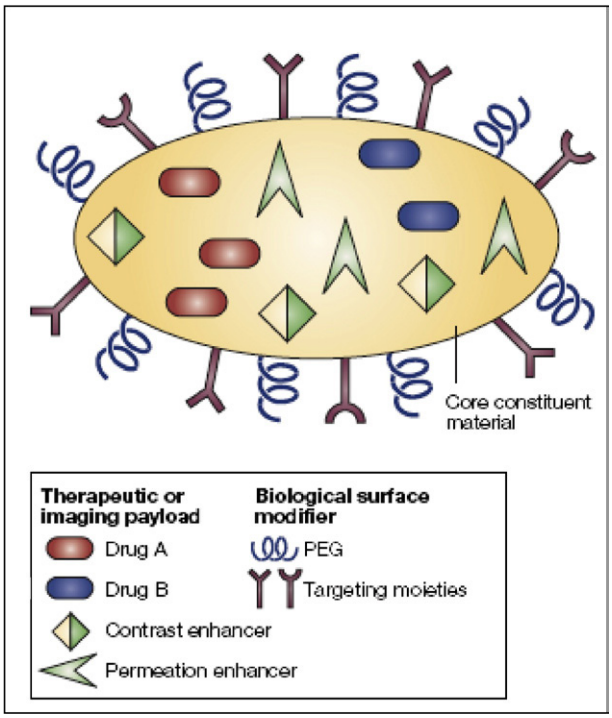

Fig. 1. Schematic illustration of multi-functional nanocarrier system. The core material of the nanocarrier can be organic (such as with liposomes and polymeric nanoparticles), inorganic (such gold nanoparticles and quantum dots) or a hybrid combination of organic and inorganic materials. The functional payload can consist of therapeutic drugs or DNA, imaging agents (such as contrast enhancers), and therapeutic adjuvants such as apoptotic modulators and drug efflux pump substrates. Surface modification can consist of poly(ethylene glycol) (PEG) or poly(ethylene oxide) (PEO) residues combined with active targeting ligands. *Reprinted with permission from Nature Reviews Cancer, 2005 © Nature Publishing Group* [2].

modality, or with energy delivery, the interaction of system components (i.e., synergy, quenching, enhanced toxicity) and release kinetics should also be considered. Surface properties are the third design component of multi-functional nanocarriers. A common surface modification technique that decreases reticuloendothelial system (RES) clearance is the physical or covalent attachment of poly (ethylene glycol) (PEG) chains to the nanocarrier platform. Since tumor microvasculature is known to be highly fenestrated, colloidal particles can accumulate by the enhanced permeability and retention (EPR) effect [3,4]. PEG surface modification increases circulatory residence time, which increases the probability of accumulation at the target. Block copolymers of poly(ethylene oxide) (PEO) and poly (propylene oxide) (PPO) (e.g., Pluronics®) have also been used as surface conjugates to enhance circulation and achieve passive targeted delivery.

3. Nanocarriers for stimuli-responsive and combination drug therapy

To achieve specificity, many drug delivery systems employ active targeting. Active targeting exploits distinguishing characteristics of target disease cells through the use of antigen targeting (antibody), carbohydrate targeting (lectins), or receptor targeting (small molecule ligands and peptides) [5]. Although there are merits to active targeting, such as enhanced efficacy, active targeting strategies can result in a high accumulation of the nanocarrier in non-disease cells due to basal expression of antigens, carbohydrates, and receptors. An alternative approach to achieving localized drug release is the use of stimuli-responsive formulations that release a therapeutic payload in response to a microenvironmental trigger. Our laboratory has explored this approach to localized drug delivery through the development of glutathione-responsive formulations (discussed in Section 5) and pH-sensitive carriers. Our pH-sensitive systems utilize a class of biodegradable cationic polymers, poly(β-amino ester)s (PbAE), where a representative hydrophobic polymer is insoluble in aqueous media at physiological pH (7.4), but rapidly dissolves below pH 6.5 [6–8]. In view of the fact that this representative PbAE is stable in the extracellular environment, but dissolves in the tumor interstitium, and upon cellular internalization in the endosomal (pH ~ 6.5) and lysosomal (pH ~ 5) compartments, they are ideal components of tumor-targeted drug and DNA delivery vehicles.

Using a solvent displacement method, as shown in Fig. 2, we have reproducibly prepared a PEO-modified PbAE nanoparticulate carrier system for the delivery of hydrophobic agents to tumors and have evaluated the system *in vitro* and *in vivo* studies [9–11]. As determined by electron spectroscopy for chemical analysis, the optimal concentration for blending the PEO surface modifier (Pluronic® F 108) with the PbAE core was 20% w/w [9]. To visualize the intracellular uptake and release kinetics, the PEO–PbAE nanocarriers were loaded with fluorescein isothiocyanate (FITC), incubated with human breast adenocarcinoma cells, and compared to pH-insensitive PEO-modified poly(ε-caprolactone) (PCL) nanoparticles [9]. Within 1 h, dissolution of the PEO–PbAE nanocarriers resulted in diffuse intracellular fluorescence; conversely, the intracellular fluorescent signal after 1 h of incubation with PEO–PCL nanoparticles was compartmentalized and diminutive [9]. To confirm the rapid release of agents from PEO–PbAE nanocarriers in acidic conditions, the formulation was loaded with tritiated paclitaxel, incubated with breast cancer cells, and compared to [^{3}H]-paclitaxel loaded PEO–PCL nanocarriers, as well as

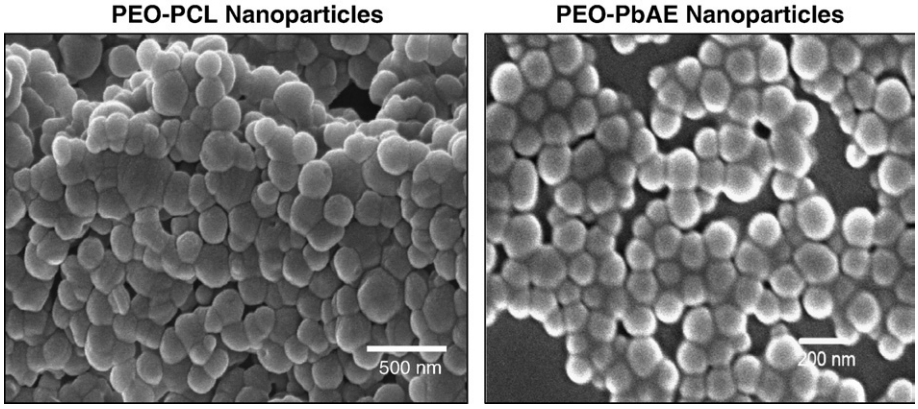

Fig. 2. Scanning electron microscopy images of poly(ethylene oxide)-modified poly(ε-caprolactone) (PEO–PCL) and PEO-modified poly(β-amino ester) (PEO–PbAE) nanoparticles. Both types of nanoparticles were prepared using a solvent displacement method.