Taylor & Francis
Taylor & Francis Group

Expert Opinion on Drug Delivery

ISSN: 1742-5247 (Print) 1744-7593 (Online) Journal homepage: http://www.tandfonline.com/loi/iedd20

Strategies for optimizing polymer-lipid hybrid nanoparticle-mediated drug delivery

Xiao Yu Wu

To cite this article: Xiao Yu Wu (2016) Strategies for optimizing polymer-lipid hybrid nanoparticle-mediated drug delivery, Expert Opinion on Drug Delivery, 13:5, 609-612, DOI: 10.1517/17425247.2016.1165662

To link to this article: http://dx.doi.org/10.1517/17425247.2016.1165662

Accepted author version posted online: 15 Mar 2016.
Published online: 04 Apr 2016.

EXPERT OPINION ON DRUG DELIVERY, 2016
VOL. 13, NO. 5, 609–612
http://dx.doi.org/10.1517/17425247.2016.1165662

Taylor & Francis
Taylor & Francis Group

EDITORIAL

Strategies for optimizing polymer-lipid hybrid nanoparticle-mediated drug delivery

Xiao Yu Wu

Advanced Pharmaceutics and Drug Delivery Laboratory, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Canada

ARTICLE HISTORY Received 3 December 2015; accepted 10 March 2016; published online 4 April 2016

KEYWORDS co-delivery of synergistic drug combination; drug-excipient interactions; formulation selection; optimization; polymer–lipid hybrid nanoparticles; spatiotemporal drug release

1. Introduction

Polymer–lipid hybrid nanoparticles (PLN) are an emerging nanoparticle drug delivery system made of polymers and lipids taking advantages of both materials. PLN are solid at body temperature, which is similar to solid lipid nanoparticles (SLN),[1,2] but different from the traditionally referred lipid-based nanoparticles – liposomes that consist of an aqueous core enclosed in a lipid bilayer. The coexistence of polymer and lipid possessing different material properties, such as hydrophobicity and water-solubility, imparts PLN versatile capability of loading varying types of payloads, which is different from SLN and nanostructured lipid carriers that are mainly for loading hydrophobic compounds. Compared to other types of nanoparticle drug carriers, PLN exhibit a number of unique advantages including (1) wide selections of biocompatible polymers and lipids and numerous polymer–lipid combinations, (2) easy fabrication by a single-step method, and (3) superior capability of co-encapsulating therapeutic and imaging agents of different properties. PLN formulations have been demonstrated to increase drug loading efficiency, enable controlled drug release, improve drug uptake and intracellular drug transport, and circumvent membrane efflux transporter-mediated multidrug resistance (MDR) in cancer cells. Like other types of nanocarriers, PLN can also be conjugated with targeting moieties for targeted drug delivery to tumor vasculature and tumor cells. Because of these advantages, PLN system is of tremendous potential for delivery of a broad range of therapeutic agents. However, it is challenging to design optimal formulations with all desirable characteristics for specific applications such as cancer chemotherapy. This editorial article provides an overview of PLN formulations with a focus on injectables for cancer therapy, representative examples, and discusses the key factors, strategies, and future in the development of PLN for effective delivery of individual or combinatorial therapeutic agents.

2. Emergence and progress of PLN development

PLN were initially devised in late 1990s and early 2000 to mitigate the problem of loading water-soluble, ionic drugs in hydrophobic solid lipid phase to achieve adequate loading and sustained release of such drugs.[1,3] Since then, various PLN formulations have been developed to encapsulate a single anticancer drug,[4] or co-encapsulate a drug with a chemosensitizer,[1,3] a drug with a P-glycoprotein (P-gp) inhibitor,[5] or dual anticancer drugs of synergy.[6] PLN formulations have also been developed to deliver biologics for gene therapy and immunotherapy, including siRNA [7] or siRNA with an anticancer drug.[8] PLN formulations have been shown to circumvent efflux transporter-mediated multidrug resistance (MDR) in cancer cells [1,4,6,9] and increase antitumor efficacy while reducing systemic toxicity of the anticancer drugs.[10,11] It was found that the PLN facilitated drug uptake and retention in P-gp overexpressing cancer cells, provided effective intracellular drug release, transported the drug (e.g. doxorubicin) to the nuclei where drug target (i.e. DNA) is located,[4,6,10] and enabled spatiotemporal co-delivery and local bioavailability of anticancer drugs in solid tumor and cancer cells.[12] Owing to these unique properties and more desired drug release kinetics than clinically used liposomal doxorubicin (Doxil®/Caelyx®) which has a long release half-life of 118 hours, a PLN formulation with co-encapsulated synergistic anticancer drugs, that is, doxorubicin and mitomycine C, outperformed Doxil®/Caelyx® in MDR cancer cells and in preclinical tumor models.[10–12]

3. Composition and design of PLN

Biocompatible polymers have been used to make PLN including poly(lactic-co-glycolic acid) (PLGA), dextran sulfate, polyethylenimine (PEI), and a polymer derived from soy bean oil. Lipids in PLN formulations are those already used in pharmaceutical products, such as phospholipids, polyethylene glycol (PEG)–lipid, extracts of food products (e.g. lecithin), or found in the body (e.g. endogenous fatty acids). Up to date, reported PLN formulations can be divided into two major categories as schematically illustrated in Figure 1: type A – monolithic matrix PLN, where polymer and drug(s) are homogeneously distributed in the solid lipid matrix,[1,3–6,9–12] and type B – core-shell PLN, where drug-containing polymer core is covered by a single layer of phospholipid.[7,8,13] The latter is sometimes called lipid–polymer hybrid nanoparticles (LPN) in literature.[7,8,13]

CONTACT Xiao Yu Wu xywu@phm.utoronto.ca

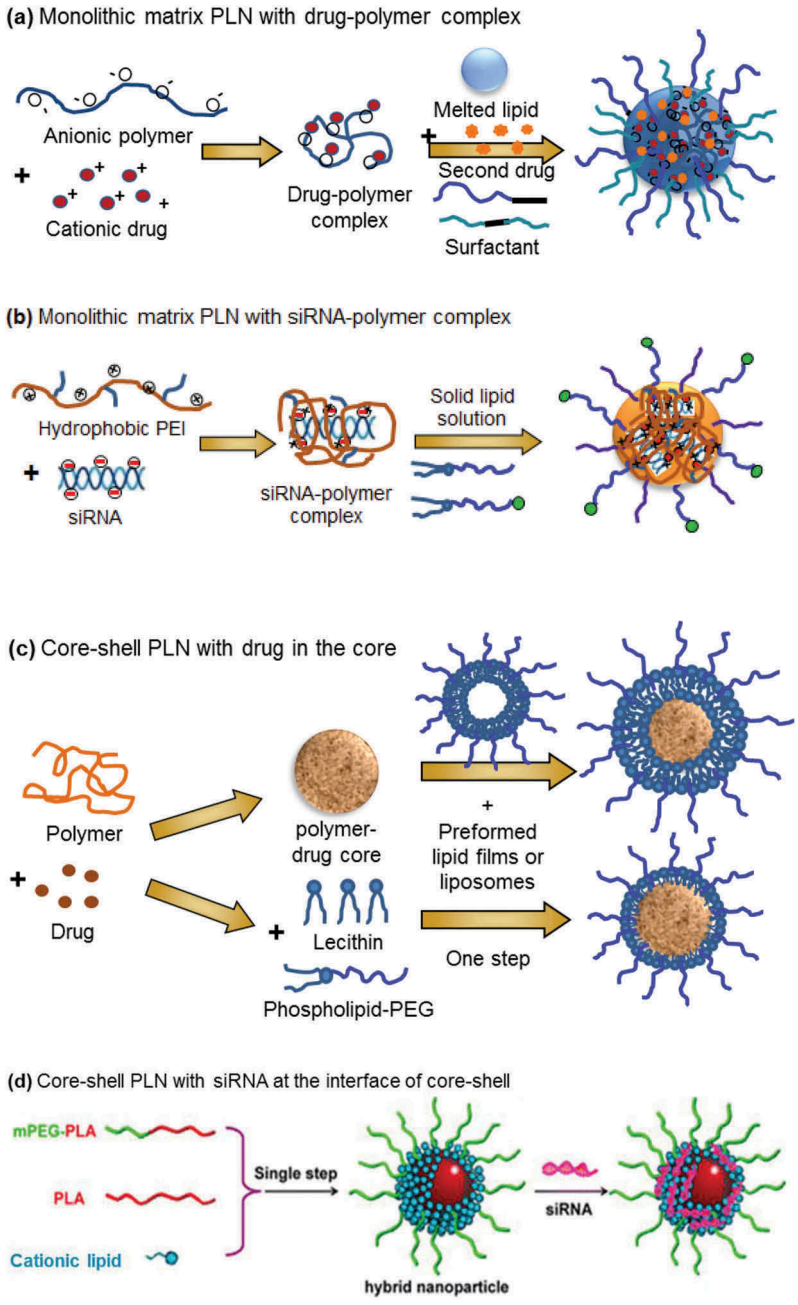

Figure 1. Schematic illustration of preparation and structures of two main types of polymer-lipid hybrid nanoparticles. (a) Monolithic matrix PLN, where polymer-drug complex with or without second drug is homogeneously distributed in the solid lipid matrix; (b) monolithic matrix PLN, where siRNA-polymer complex is distributed in the solid lipid matrix and the surface is decorated with targeting moieties; (c) core-shell PLN, where the core is comprised of polymer and drug in a solid matrix core and the shell is formed by phospholipid and phospholipid-PEG; (d) core-shell PLN, where the core is made of PLA, the shell is formed by mPEG-PLA, and siRNA is loaded by complexation with the cationic lipid at the interface of the core and the shell. (d) is adapted with permission from [7].

Figure 1(a) and (b) portray the representative components and procedures used for preparation of type A PLN formulation for cationic drug (a) or anionic siRNA (b). For loading a cationic drug, for example, doxorubicin HCl or verapamil HCl, an anionic polymer, such as dextran sulfate or hydrolyzed polymer of epoxidized soybean oil was employed to neutralize the charge of the drug and bring the drug to melted lipid phase. After ultrasonication of the polymer–drug complex with the melted lipid in the presence of surfactants, for example, Tween 80 and Pluronic F68, or lipid–PEG, the emulsion was then cooled in a cold aqueous medium forming solid PLN. Type A PLN can be prepared in one-pot with a little or no organic solvent. The second drug or both drugs can be non-ionic and hydrophobic (e.g. Elacridar). Drug loading content and loading efficiency can be maximized and drug release kinetics can be tailored by rational selection of type of lipid and polymer and lipid to polymer ratio.[13,14,15] The drug to lipid ratio and cosurfactant concentration and ratio were optimized to obtain desirable loading efficiency and particle size. [15] In cases of loading hydrophobic drug(s) only, a hydrophobic polymer, for example, PLGA, can be used with lipid to form PLN, which is more straightforward as the polymer and lipid would be quite miscible. By utilizing cationic polymers, for example, chitosan and PEI, anionic drugs and biologics,

such as DNA and siRNA can be encapsulated in PLN. The wide selections of polymers, lipids, and their combinations render type A PLN tremendous versatility for single delivery or co-delivery of a variety of payloads ranging from small molecules to macromolecules and from water-soluble drugs to poorly water-soluble drugs. Moreover, type A PLN can be made 'stealth' for prolonged systemic circulation by introducing PEG–lipid of two different chain lengths.[6,9–12]

The core-shell (type B) PLN utilize the advantage of hydrophobic polymer core for sustained drug release and lipid (bi) layer to mimic hydrophilic liposomal surface. PEG chains can also be conjugated on the surface to achieve long circulation of the nanoparticles. Type B PLN are normally prepared by a two-step method (Figure 1(c) top). The drug-loaded polymer core is synthesized by oil-in-water emulsion and solvent evaporation, where a hydrophobic polymer, for example, PLGA is dissolved in an organic solvent together with the drug. The prepared drug-loaded polymer core is then mixed with rehydrated, preformed lipid film or liposomes to form lipid bilayer or multilayer-coated polymer nanoparticles. A new one-step nanoprecipitation method was developed to make lipid monolayer-coated polymer–drug core PLN (Figure 1(c) bottom).[13] In this experiment, ester-terminated PLGA and drug were dissolved in acetonitrile, while lecithin and phospholipid-conjugated PEG in heated ethanol and water. The PLGA-drug solution was dropwise added to the surfactant solution, vortexed, stirred and formed type B PLN by self-assembly.[13] Figure 1(d) portrays another example of type B PLN where siRNA was loaded at the interface between polymer core and cationic lipid in the shell by ionic complexation.[7]

4. Expert opinion

The ultimate goal of research in PLN-mediated drug delivery is to develop effective and safe therapy for clinic use. Development of PLN formulations with increased efficacy and reduced toxic side effects is particularly important for improving cancer therapy where toxicity is always associated with therapeutic efficacy. Over the past 15 years, the field of PLN-mediated drug delivery has been developed quickly to achieve this goal. All reported PLN formulations are made by simple preparation methods from polymers, lipids, and surfactants that have been used in approved pharmaceutical products, or are generally regarded as safe (GRAS). This mentality in the field is healthy and crucial for translating preclinical results to nanomedicines that can benefit millions of people suffered from cancer and other diseases. Use of pharmaceutical and GRAS excipients would accelerate product development by removing one hurdle to regulatory approval of the products. Therefore, it is expected to see PLN formulations being moved to clinical trials in the next few years.

Combining different properties of diverse polymers and lipids in PLN presents a tremendous opportunity for development of PLN to suit various drug delivery needs, especially for combination therapies via co-delivery of multiple agents of distinct properties. The research in the field has already demonstrated the unique advantages and great potential of PLN platform, which will warrant further development of PLN formulations for clinic use. Successful design of PLN formulations requires comprehensive consideration of basic properties of nanoparticle drug carriers, that is, drug loading capacity, loading efficiency, particle size, surface charge, colloidal stability, and spatiotemporal drug release. These properties can be optimized by rational selection of polymer, lipid, surfactant, and their relative ratios by theoretical calculations, physicochemical characterization, and optimization tools.[14,15] Physicochemical compatibility and affinity are essential for efficiently loading the drug into PLN and precisely controlling drug release kinetics. Hence, thorough understanding of material properties in relation to physicochemical properties of PLN is beneficial for successful design of PLN.

For delivering anticancer agents to solid tumors via systemic injection, spatiotemporal drug release from PLN is critical as it directly impacts the efficacy and toxicity of the treatment. However, current techniques for measuring drug release kinetics of nanoparticles are inaccurate for *in vitro* test and virtually impossible for *in vivo* test. Conventional pharmacokinetic measurement of drug concentration in plasma and organs could not correlate well with therapeutic efficacy, typified by liposomal doxorubicin (Doxil®/Caelyx®), as it fails to distinct released drug from unreleased drug. Because only the released drug, instead of total amount of drug in the tumor, is bioavailable for generating therapeutic effects,[12] it is important to seek advanced technologies for evaluating *in vivo* drug release, local bioavailability, and therapeutic response.

An exciting and interesting application of PLN is delivery of synergistic drug combinations. The multiple components in PLN impart them capability of loading multiple agents in one carrier and releasing the payloads at different times and intracellular locations. Good knowledge about how biological systems process polymers, lipids, and surfactants, and about mechanisms of drug action could help optimal design of PLN. For example, by tailoring the structure and material of PLN, siRNA can be released in cytoplasm rapidly while a co-delivered anticancer drug being released in nuclei slower.[7,8]

Declaration of interest

This work is supported in part by the Canadian Breast Cancer Foundation-Ontario Region. The author states no conflict of interest and has received no payment in preparation of this manuscript. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1. Wong HL, Rauth AM, Bendayan R, et al. Chemotherapy with anticancer drugs entrapped in solid lipid nanoparticles. Adv Drug Delivery Rev. 2007;59:491–504.
2. Müller RH, Mäder K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery – a review of the state of the art. Eur J Pharm Biopharm. 2000;50:161–177.
3. Wong HL, Bendayan R, Rauth AM, et al. Development of solid lipid nanoparticles containing ionically-complexed chemotherapeutic drugs and chemosensitizers. J Pharm Sci. 2004;93:1993–2008.

•• **Developed the first version of PLN made by using anionic polymer to facilitate loading of cationic antineoplastic agents and chemosensitizers in solid lipid nanoparticles and delivering multiple drugs in one PLN for treatment of drug resistant tumors**.

4. Wong HL, Rauth AM, Bendayan R, et al. A new solid lipid nanoparticle formulation increases cytotoxicity of doxorubicin against multidrug-resistant human breast cancer cells. Pharm Res. 2006;23:1574–1585.
5. Wong HL, Bendayan R, Rauth AM, et al. Simultaneous delivery of doxorubicin and GG918 (Elacridar) by new polymer-lipid hybrid nanoparticle (PLN) formulations for combinational treatments of multidrug-resistant breast cancer. J Control Release. 2006;116:275–284.
6. Shuhendler AJ, Cheung R, Manias J, et al. A novel doxorubicin-mitomycin C co-encapsulated nanoparticle formulation exhibits anti-cancer synergy in multidrug resistant human breast cancer cells. Breast Cancer Res Treat. 2010;119:255–269.

•• **Developed the first "stealth" PLN with co-loaded synergistic anticancer drugs doxorubicin and mitomycin C**.

7. Yang X-Z, Dou S, Wang Y-C, et al. Single-step assembly of cationic lipid-polymer hybrid nanoparticles for systemic delivery of siRNA. ACS Nano. 2012;6:4955–4965.
8. Zhao X, Li F, Li Y, et al. Co-delivery of HIF1alpha siRNA and gemcitabine via biocompatible lipid-polymer hybrid nanoparticles for effective treatment of pancreatic cancer. Biomaterials. 2015;46:13–25.
9. Prasad P, Cheng J, Shuhendler AJ, et al. A novel nanoparticle formulation overcomes multiple types of membrane efflux pumps in human breast cancer cells. Drug Delivery Transl Res. 2012;2:95–105.
10. Prasad P, Shuhendler AJ, Cai P, et al. Doxorubicin and mitomycin C co-loaded polymer-lipid hybrid nanoparticles inhibit growth of sensitive and multidrug resistant human mammary tumor xenografts. Cancer Lett. 2013;334:263–273.
11. Shuhendler AJ, Prasad P, Zhang RX, et al. Synergistic nanoparticulate drug combination overcomes multidrug resistance, increases efficacy, and reduces cardiotoxicity in a non-immunocompromised breast tumor model. Mol Pharm. 2014;11:2659–2674.
12. Zhang RX, Cai P, Zhang T, et al. Polymer-lipid hybrid nanoparticles synchronize pharmacokinetics of co-encapsulated doxorubicin-mitomycin C and enable their spatiotemporal co-delivery and local bioavailability in breast tumor. Nanomed-NBM. 2016; published online first Jan 7 2016. DOI:10.1016/j.nano.2015.12.383.
13. Zhang L, Chan JM, Gu FX, et al. Self-assembled lipid–polymer hybrid nanoparticles: a robust drug delivery platform. ACS Nano. 2008;2:1696–1702.

• **Demonstrated higher drug encapsulation yield and less initial burst of drug (docetaxel) release when a lipid (lecithin) and lipid–PEG were used together with PLGA to form hybrid nanoparticles**.

14. Li Y, Taulier N, Rauth AM, et al. Screening of lipid carriers and characterization of drug-polymer-lipid interactions for the rational design of polymer-lipid hybrid nanoparticles (PLN). Pharm Res. 2006;23:1877–1887.

•• **Screened a variety of lipids by comparing their solubility parameters with the drug and polymer–drug complex and by measuring partition of polymer–drug complex in lipids. The lipid with the maximum miscibility with the polymer–drug complex was selected for making the PLN**.

15. Li Y, Abbaspour MR, Grootendorst PV, et al. Optimization of controlled release nanoparticle formulation of verapamil hydrochloride using artificial neural networks with genetic algorithm and response surface methodology. Eur J Pharm Biopharm. 2015;94:170–179.

•• **Applied optimization tools to find an optimal PLN formulation that resulted in desirable particle size and drug loading efficiency**.