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Review

# Biocompatible polymersomes-based cancer theranostics: Towards multifunctional nanomedicine

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ABSTRACT

Polymersomes are polymeric vesicles that have numerous advantages for theranostics, the integrated approach of therapeutics and diagnostics. Polymersomes possess core- shell structures which encapsulate hydrophilic molecules in the aqueous compartment and hydrophobic molecules in the bilayer of the vesicles. Polymersomes are made of different amphiphilic block copolymers. Thus, in the process of designing polymersomes, a variety of amphiphilic block copolymers with different molecular weights are used to develop intelligent or sustained released formulations and to modify the stability of the system and bilayer thickness or to functionalize the particle with targeting moieties to improve the delivery efficiency.

In addition, biocompatible and/or biodegradable polymersomes are diverse in size and charge which show low toxicity *in vivo*. Polymersomes are increasingly being used as platforms for simultaneous drug delivery and imaging and are therefore becoming popular theranostic nanoparticles. This review focuses on the methods of nanoparticle formation when polymersomes for theranostic nanomedicine are engineered. We highlight recent examples of polymersome theranostic systems from literature and their potential for use in the clinic, particularly biodegradable or biocompatible-based NPs.



**Contents**



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## 1. Introduction

Although big steps towards preparation of novel formulations for anticancer agents have been made in the recent years, cancer is still one of the important public health problems worldwide. Conventional chemotherapy agents cause serious adverse effects due to the nonspecific distribution, insufficient delivery to the tumor site and consequently severe toxicity (Bleul et al., 2013).

Medical nanotechnology is moving towards overcoming challenges and pitfalls in drug delivery platforms to optimize drug delivery systems in terms of controlled and sustained release, encapsulation efficiency, stability in biological media and bioavailability of the cargos. Nanoparticulate drug delivery to cancer cells demonstrates long circulating carriers to facilitate entering tumor environment via passive mechanisms. Liposomes are the frontrunner carriers for drug delivery due to their long clinical applications and well established characteristics (Chang et al., 2014). Stealth liposomes made of polyethylene glycol (PEG) coated liposomes showed increased blood circulation time for up to 2–3 days after intravenous injection (Cattel et al., 2002). Biodegradable polymersomes which are self-assembled polymeric vesicles made of biodegradable amphiphilic block copolymers containing hydrophilic and hydrophobic blocks have superior physicochemical properties over liposomes including high stability, prolonged circulation time (up to two-fold more than PEGylated liposomes), biodegradability and sustained release of drug (Li et al., 2015d). These vesicles show slow dissociation and long retention of the payload which is due to low critical micelle concentrations and slow chain exchange dynamics for amphiphilic block copolymers (Li et al., 2015d). It is demonstrated that mechanical stability of vesicles is related to their membrane thickness (Opsteen et al., 2004). The membrane thickness of polymersomes could be several folds more than liposomes as molecular weight of block copolymers is higher than phospholipids (Chandrawati and Caruso, 2012) which provides higher colloidal stability against osmotic pressure and mechanical shear in blood circulation (Cho et al., 2010) leading to less permeability of polymersomes to water-soluble molecules in comparison with liposomes. Previously it was demonstrated that Doxil$^{R}$ (FDA-approved nanoliposomal doxorubicin) possesses slow release profile of the entrapped drug in the tumor tissue and the major cause of drug release is the destabilization of liposomes by phospholipases present in the tumor environment (Nikpoor et al., 2015). An added advantage of biodegradable polymersomes is that the stability or the release profile of the formulation could be tailored by tuning the block copolymers which could be made of different synthetic polymers with wide range of molecular weights and physic-chemical characteristics. Rather than the slow release profile of Doxil, another important issue about liposomal formulations is the high cost of lipid raw materials used for liposomal preparations (Barenholz, 2001; Kulkarni et al., 2011) compared to synthetic block copolymers of polymersomes.

Moreover, the synthetic nature of polymersomes provides greater flexibility to modulate polymersome response to external stimuli such as oxidative stress, pH, temperature and enzymatic degradation (Chandrawati and Caruso, 2012) and facilitates designing of multifunctional platforms.

Polymeric micelle is another amphiphilic block copolymer nanoparticulate structure produced by self-assembly of amphiphilic block copolymers in aqueous media over the amphilile critical micelle concentration (CMC) (Letchford and Burt, 2007). In contrast to liposomes and polymersomes which are able to encapsulate both hydrophobic and hydrophilic agents within the bilayer and the aqueous compartment of the vesicles (Levine et al., 2008), polymeric micelles have been used as delivery vehicles for hydrophobic agents (Xu et al., 2013).

Earlier it was proved that linear amphiphilic copolymers with hydrophilic volume fraction ($f_{EO}$) greater than 50% are expected to form micelles whereas polymersomes are formed at $25\% < f_{EO} < 40\%$ (Alibolandi et al., 2015a,b,c). Then due to the lower volume fraction of hydrophobic section in micelle structures in comparison with polymersomes, they show higher CMC leading to lower stability in biological environments (Kim et al., 2010).

Previously, we extensively compared the micelles and polymersomes structures. In this regard amphiphilic diblock copolymers made of hydrophilic poly-ethyleneglycol (PEG, 5000 Da) and hydrophobic poly(D,L lactic acid) (PLA, 15000 Da and 5000 Da) with the sizes of PEG5000-PLA15000 and PEG5000-PLA5000 were synthesized in order to produce polymersomes and micelles structures respectively. In the next stage, the stability, release profile and encapsulation capacity of the hydrophobic doxorubicin loaded structures were investigated.

Due to the fact that the PLA blocks in (PEG-PLA 5000:15000 Da) is too bulky to fit in the interior of the micelle, the bilayer sheet is formed in which PLA chains are oriented towards inside of the bilayer and PEG chains face the aqueous compartment. Obtained results exhibited that loading capacity and encapsulation efficiency of the polymersomes were higher than micelles which might be due to greater size of polymeric vesicles (150 nm) compared to micelles (50 nm) and higher molecular weight of hydrophobic section (PLA block) in polymersome structures. Moreover, the release rates of doxorubicin from micelles were faster than polymersomes due to shorter hydrophobic block of micelles which causes easier water penetration into the core of nanoparticles and its aggregation which leads to instability of micelles structures (Alibolandi et al., 2015c).

Recently, simultaneous therapeutic and diagnostic approaches have opened the new venue in nanomedicine research area named “theranostic nanomedicines” in which nanocarriers are capable of transporting antineoplastic and diagnostic agents to the tumor tissues for combined drug delivery and real time monitoring of disease progression and/or the biological response to the carried drug (De Oliveira et al., 2012; Chiang et al., 2013). This powerful technique provides uncompromised detection ability of cancer in early stages. In another words, theranostics are ideal strategy for cancer therapy and treatment response evaluation (Table 1).

There are tremendous researches on development of nanoscale theranostics systems.

In this review, we summarized the preparation methods of polymersomes for codelivery applications. Then, we focused on theranostics and also diagnostic polymersomes which can be used for theranostics purposes in the future, based on various imaging probes for MRI, ultrasound, optical and surface plasmon resonance (SPR) imaging.

## 2. How to design and prepare polymersomes with desirable characteristics for co-delivery?

In this section, we highlight some of the nanostructures preparation methods, which led to the formation of polymersomes for co-delivery applications and show promise for controlled release of encapsulated agents (Discher et al., 1999; Discher and Eisenberg, 2002).

For the first time, Hammer and Discher developed polymersomal structures. They used poly(ethylene oxide)-*block*-poly(ethylethylene) (PEO-*b*-PEE) diblock copolymers to self-assemble in aqueous environments, and characterized the physical properties of the polymersomal structures (Discher et al., 1999).

Previously it was verified that when the solution concentration of an amphiphilic block copolymer is above the critical aggregate concentration (CAC), it can self-assemble to form the aggregates with high molecular weights. Critical aggregate concentration