Available online at www.sciencedirect.com
ScienceDirect
Prog. Polym. Sci. 32 (2007) 838–857
PROGRESS IN POLYMER SCIENCE
www.elsevier.com/locate/ppolysci

Emerging applications of polymersomes in delivery: From molecular dynamics to shrinkage of tumors

Dennis E. Discher[a,*], Vanessa Ortiz[b], Goundla Srinivas[b], Michael L. Klein[b], Younghoon Kim[a], David Christian[a], Shenshen Cai[a], Peter Photos[a], Fariyal Ahmed[a,1]

[a]*NanoBio Polymers Lab, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA*
[b]*Center for Molecular Modeling, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA*

Received 17 April 2007; received in revised form 24 May 2007; accepted 24 May 2007
Available online 8 June 2007

Abstract

Polymersomes are self-assembled shells of amphiphilic block copolymers that are currently being developed by many groups for fundamental insights into the nature of self-assembled states as well as for a variety of applications. While recent reviews have highlighted distinctive properties—particularly stability—that are strongly influenced by both copolymer type and polymer molecular weight, here we first review some of the more recent developments in computational molecular dynamics (MD) schemes that lend insight into assembly. We then review polymersome loading, *in vivo* stealthiness, degradation-based disassembly for controlled release, and tumor shrinkage *in vivo*. Comparisons of polymersomes with viral capsids are shown to encompass and inspire many aspects of current and emerging designs.

Keywords: Liposomes; Amphiphile; Block copolymers; Nano-particles; Controlled release

Contents

*Corresponding author.
E-mail address: discher@seas.upenn.edu (D.E. Discher).
[1]Current address: CBRI, Harvard Medical School.

0079-6700/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.progpolymsci.2007.05.011

1. Introduction

Viral capsids are perhaps the prototypical 'supramolecular assemblies for hollow structures', which is the inspired theme for this collection of reviews that includes the review here on 'polymersomes'. Viral capsids self-assemble from polypeptides and serve to contain the virus' genome, thereby protecting the nucleic acid from degradation. The robust capsid shells also integrate delivery mechanisms with viral targeting and controlled release. Polymersomes are likewise self-assembled—but from synthetic polymers rather than peptide-based polymers, and these synthetic shells are now being engineered to perform some of the same functions as robust viral capsids, namely to carry, protect, target, and release actives (drugs, nucleic acids, and dyes).

For both viruses and now polymersomes, structurally detailed models of assembly and disassembly are emerging and should provide deeper insight into energetics as well as mechanisms of loading and delivery of nucleic acid or drug. Both modeling and delivery aspects of polymersomes are our dual focus in this integrated review. As recently summarized [1], the selection of synthetic polymer(s) and especially the choice of molecular weight (M) of the polymers used for polymersomes are critical since these impart the vesicular shells with a broad range of tunable carrier properties.

Amphiphilicity is exploited for polymer vesicle assembly. Nature's own vesicle-forming amphiphiles are of course lipids that almost always possess $M < 1$ kDa (Fig. 1A), whereas vesicle-forming polymers are invariably much larger. The copolymers used have at least one hydrophilic fraction or 'block' linked to a hydrophobic block that is as large or larger. Either type of amphiphile, lipid or block copolymer, if made with suitable amphiphilic proportions, can self-direct its collective assembly into closed vesicles upon hydration of a cast film. Heat and sometimes cosolvent are needed to fluidize the films, but the hydrophobic blocks of each molecule have an intrinsic tendency to aggregate and minimize direct exposure to water while the more hydrophilic blocks form inner and outer brushes that are well hydrated and define or delimit the inner and outer interfaces of a typical bilayer vesicle.

As derived from nature, lipids tend to be biocompatible, which has partially motivated broad efforts to develop liposomes into drug carriers over the last several decades. However, liposomes lack controlled release mechanisms among a number of other pharmacokinetic limitations. These include a limited circulation in the body of hours or less, which minimizes the likelihood of delivering drug to an intended target site. This shortcoming was first addressed about two decades ago by adding a hydrated polymer layer on the liposome that some would describe as a mimic of the carbohydrate coat or glycocalyx on cell membranes. This mimickry is most commonly achieved through attachment of biocompatible polyethylene glycol (PEG) (or polyethylene oxide (PEO)) to a small fraction (5–10%) of the lipid headgroups, as reviewed further below. Over the last decade, a range of PEO-based diblock copolymers have emerged that eliminate the need for lipid in vesicle formation. Promising biocompatible copolymers include PEO plus degradable chains, such as PEO–polylactic acid (PEO–PLA) and PEO–polycaprolactone (PEO–PCL), which are not only being widely synthesized to make polymersomes but are also now commercially available off-the-shelf or custom synthesized, broadening accessibility for a new generation of researchers.

Cells are no doubt capable of synthesizing superamphiphilic compounds similar in size and form to the diblocks described here, but the low M of natural lipids imparts biomembranes with lateral fluidity and other "soft" properties [1] that are no doubt conducive to various cellular processes (endocytosis, cell division, receptor clustering, etc.). Fluidity does not seem necessary for viral capsids but genome protection is essential, and so nature has switched to the lock-and-key assembly of proteins. Capsid proteins are polypeptides with a typical M in the range of 10–20 kDa or higher,