Advanced Drug Delivery Reviews 64 (2012) 811–825

Contents lists available at SciVerse ScienceDirect

Advanced Drug Delivery Reviews

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

Virus-based nanocarriers for drug delivery ☆

Yujie Ma [a,b], Roeland J.M. Nolte [b,*], Jeroen J.L.M. Cornelissen [a]

[a] Group of Biomolecular Nanotechnology, MESA+ Institute for Nanotechnology, University of Twente, P.O. Box 217, 7500 AE Enschede, The Netherlands
[b] Institute for Molecules and Materials, Radboud University Nijmegen, Heyendaalseweg 135, 6525 AJ Nijmegen, The Netherlands

ARTICLE INFO

Article history:
Received 28 November 2011
Accepted 12 January 2012
Available online 20 January 2012

Keywords:
Virus
Virus-like particle (VLP)
Drug delivery
Bioconjugation
Supramolecular chemistry
Targeting

ABSTRACT

New nanocarrier platforms based on natural biological building blocks offer great promises in revolutionalizing medicine. The usage of specific protein cage structures: virus-like particles (VLPs) for drug packaging and targetted delivery is summarized here. Versatile chemical and genetic modifications on the outer surfaces and inner cavities of VLPs facilitate the preparation of new materials that could meet the biocompatibility, solubility and high uptake efficiency requirements for drug delivery. A full evaluation on the toxicity, biodistribution and immunology of these materials are envisaged to boost their application potentials.

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Approaches to drug delivery based on the principles of supramolecular chemistry".

* Corresponding author. Tel.: +31 243652143; fax: +31 243652929.
E-mail address: r.nolte@science.ru.nl (R.J.M. Nolte).

0169-409X/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.addr.2012.01.005

1. Introduction

1.1. Development of nanocarrier platforms for drug delivery and targeting

With the recent rapid development of nanotechnology, advances in protein engineering and materials science are offering great promises to revolutionize medicine [1]. New nanocarrier platforms exhibiting great potentials in improving drug packaging, delivery, and targeting efficiencies are currently emerging. These systems could offer several advantages, e.g. (*i*) prevention of premature drug degradation or interaction with its biological environment, (*ii*) enhancement of drug adsorption to the desired tissues (e.g. tumors,) and (*iii*) control over the drug tissue distribution profile [1]. Examples of nanocarrier platforms that have been extensively studied include dendrimers [2], liposomes [3], polymersomes [4], micelles [5], and virus-like particles [6]. Each of these systems has its advantages and disadvantages regarding the versatile requirements for therapeutic applications. From a material point of view, the range of building blocks that can be applied for various nanocarrier platforms has been extended enormously over the past few decades. Following explorations on the design and synthesis of small compounds and polymers as well as the self-assembly of these synthetic systems, scientists are now also focusing on the direct use of natural, i.e. biological building blocks for the fabrication of nanocarriers. At the same time the investigation of self-assembly at all length scales has also proceeded to the stage of mimicking biological entities by studying hierarchical assembly behavior. All of these new developments are aimed at improving the performance of drug nanocarriers, in making them more biocompatible, water-soluble, or colloidal, displaying reduced toxicity and high differential uptake efficiencies [1].

1.2. Biological nanocontainers composed of protein cages

Protein cages are perfect examples of nanocarrier platforms built from natural materials by a process of hierarchical (supramolecular) assembly. One of the characteristic features of protein cage structures is their size uniformity, i.e. each cage exhibits an extremely homogeneous size distribution. Nature has developed a variety of protein cages with diverse sizes as nanocarriers for metal ions and minerals, which has inspired researchers to design new systems for drug packaging and delivery based on these materials. Protein cages can be chemically or biologically engineered in many ways, making them uniquely attractive platforms for drug delivery applications. One of the most famous examples is the iron storage protein ferritin. Ferritins are produced in almost all living organisms, including bacteria, plants, and animals. They consist of a central core of hydrated iron (III) oxide encapsulated within a 24-subunit protein shell. The use of ferritin's cage structure was first explored in the area of biomineralization [7]. A later approach involved the biomedical application of ferritin as a delivery vehicle for the MRI contrast agent Gadolinium (Gd) [8].

Another extensively studied biological cage structure is the small heat shock protein (sHsp). sHsp originates from the species *Methanococcus jannaschii* and consists of 24 subunits that self-assemble into a cage with a 12 nm outer diameter and a 6.5 nm inner diameter [9]. sHsp differs from ferritin in that it has large 3 nm pores that allow the free exchange of substances between the interior and exterior environments [10]. sHsp has been studied for the encapsulation and release of the antitumor agent doxorubicin (Dox) [11]. Recently, the use of sHsp as a MRI contrast agent with extremely efficient relaxivity [12] and as a vehicle for the targeted delivery of imaging agents for the diagnosis of atherosclerosis [13] has been reported, highlighting their great potential in biomedical applications.

Other examples of biological cage structures include *Lumazine synthase* (LS) [14], a hollow icosahedral bacterial enzyme and vaults [15], which are self-assembled ribonucleoprotein nanocapsules found in nearly all eukaryotic cells. However, the application potential of these compounds is yet to be evaluated.

This review will mainly focus on drug delivery applications based on a specific and important type of protein cages, i.e. viruses. Viruses, especially bacterial viruses or bacteriophages, are the most abundant

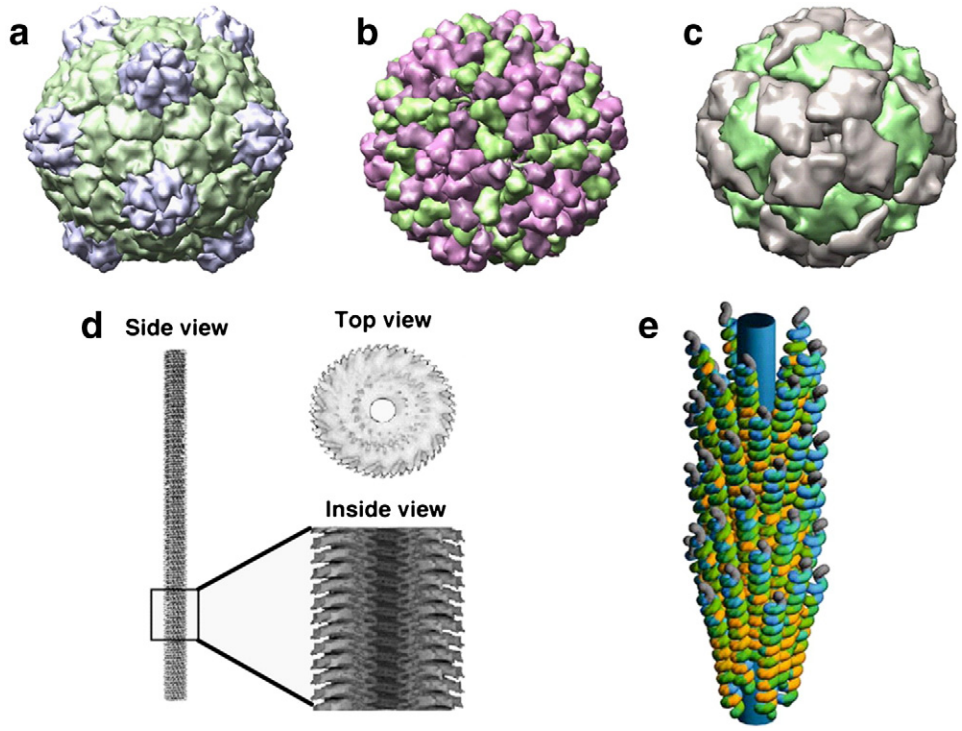

Fig. 1. Structures of some of the viruses discussed in this review: a) Cowpea mosaic virus (CPMV), 31 nm in diameter; b) Cowpea chlorotic mottle virus (CCMV), 28 nm in diameter; c) bacteriophage MS2, 27 nm in diameter; d) tobacco mosaic virus (TMV), 18 nm in diameter and 300 nm in length [19]; e) bacteriophage M13, 6.5 nm in diameter and 900 nm in length [20]. a)–c) were obtained from the RCSB protein data bank (www.pdb.org).