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Research review paper

Dendritic core–shell systems as soft drug delivery nanocarriers

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ABSTRACT

Unimolecular micelles are covalently bound molecular architectures and therefore highly stable which makes them particularly attractive for drug delivery. Accordingly, many reports in the literature emphasize the importance of these molecular architectures for nanomedicine. This conceptual review will present some of the recent advances in the application of these dendritic core–shell systems for drug delivery. Unimolecular micelles based on hyperbranched and dendritic cores will be discussed and sorted by the nature of their core and structure.

Contents

1. Introduction

The poor solubility of many newly developed drugs strongly limits their application, because only very low concentrations can be applied (Gupta et al., 2006; Kesharwani et al., 2014; Torchilin, 2001). The use of nanocarriers can improve these solubility issues and improve the therapeutic index for example, by longer blood circulation times and targeted delivery (Khandare et al., 2012; Kiparissides and Kammona, 2013; Nishiyama and Kataoka, 2006; Rawat et al., 2006; Sawant and Torchilin, 2012; Y. Zhang et al., 2014). Macromolecular polymer therapeutics benefit from the so-called enhanced permeability and retention (EPR) effect, which describes a passive accumulation of the macromolecular nanocarriers in tumor tissue (Dawidczyk et al., 2014; Haag and Kratz, 2006; Maeda et al., 2013; Zoabi et al., 2013). Active targeting moieties can be added to the macromolecular architectures as well (Chen et al., 2014; Danhier et al., 2010; Dawidczyk et al., 2014; Kedar et al., 2010; Mahmud et al., 2007). A goal in the field of polymer therapeutics is to combine these advantages (Duncan, 2011; Duncan and Vicent, 2013; Haag and Kratz, 2006). With the result that many different types of nanocarriers have been developed over the past decades, including dendrimers (Ambade et al., 2005; Aulenta et al., 2003; Caminade and Turrin, 2014;

Abbreviations: BBB, blood–brain-barrier; bis-MPA, 2,2-bis (methylol) propionic acid; CAC, critical aggregation concentration; cmc, critical micelle concentration; CMS, core–multishell; CS, core–shell; dPG, dendritic polyglycerol; EPR, enhanced permeability and retention; ITC, isothermal titration calorimetry; ITCC, tetrasulfonated indotricarbocyanine; M_n, number-averaged molecular weight; mPEG, poly(ethylene glycol) monomethyl ether; MW, molecular weight; PAMAM, Polyamidoamine; PE, polyethylene; PEG, poly(ethylene glycol); PEI, polyethyleneimine; PG, polyglycerol; PLA, poly(L-lactide); PS, polystyrene; PCL, polycaprolactone; PDLLA, poly(D,L-lactide); PLF, poly(L-phenylalanine); PLL, poly(L-lysine); PPEP, poly(2-isopropoxy-2-oxo-1,3,2-dioxaphospholane); PLG, poly(L-glutamicacid); HEEP, 2-(2-hydroxyethoxy)ethoxy-2-oxo-1,3,2-dioxaphospholane; PDEA, poly(2-(N,N-diethylamino)ehtyl methacrylate); ROMBP, ring-opening multibranching polymerization; RTCA, real-time cell analysis.

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D'Emanuele and Attwood, 2005; Duncan and Izzo, 2005; Gupta et al., 2006; Jain and Gupta, 2008; Kesharwani et al., 2014; Lee et al., 2005; Mintzer and Grinstaff, 2011; Patri et al., 2002; Quadir and Haag, 2012; Svenson, 2009; Svenson and Tomalia, 2005; Tekade et al., 2009; Zhu and Shi, 2013), micelles (Aliabadi and Lavasanifar, 2006; Deng et al., 2012; Jones and Leroux, 1999; Kedar et al., 2010; Kore et al., 2014; Mahmud et al., 2007; McLaughlin et al., 2013; Nishiyama and Kataoka, 2006; Nishiyama et al., 2005; Oerlemans et al., 2010; Qiu et al., 2007; Torchilin, 2004), vesicles (Brinkhuis et al., 2011; Discher and Eisenberg, 2002; Feng and Yuan, 2014; Lee and Feijen, 2012; Pawar et al., 2013; Xing et al., 2013), liposomes (Allen and Cullis, 2013; Chang and Yeh, 2012; Eldar-Boock et al., 2013; Mozafari et al., 2009; Schroeder et al., 2009; W. Gao et al., 2013), nano- and microgels (Alvarez-Lorenzo and Concheiro, 2014; Asadian-Birjand et al., 2012; Chacko et al., 2012; Fleige et al., 2012a; Kabanov and Vinogradov, 2009; Nowag and Haag, 2014; Oh et al., 2008, 2009; Talevi et al., 2014; Tong et al., 2014; Yallapu et al., 2011), and others (Alvarez-Lorenzo and Concheiro, 2014; Couvreur, 2013; Kiparissides and Kammona, 2013; Moosa et al., 2014; Mora-Huertas et al., 2010; Mozafari et al., 2009; Musyanovych and Landfester, 2014; Rawat et al., 2006; Safari and Zarnegar, 2014; Singh and Lillard, 2009; Timko et al., 2011). Apart from the widely studied amphiphilic block copolymers (Gaucher et al., 2005; Kataoka et al., 2001, 2012; Rösler et al., 2012; Torchilin, 2005; Xiong et al., 2011), core–shell architectures have also gained considerable attention (Han and Gao, 2011; Hayes et al., 2014; Ramli et al., 2013). Core–shell architectures have been synthesized using many different materials based on organic as well as inorganic compositions (Chatterjee et al., 2014; Ghosh Chaudhuri and Paria, 2012; Ma et al., 2013). Smart polymeric core–shell systems offer a way to obtain tailor-made properties by employing advanced polymerization techniques, which can lead to controlled architectures. In this context, different types of covalent polymeric core–shell systems have to be mentioned. The core can be either cross-linked, star molecules, or dendritic including perfect dendrimers as well as hyperbranched polymers. Excellent reviews have been recently published about the first two kinds of polymeric core–shell nanocarriers (Gao, 2012; Kedar et al., 2010; Talelli et al., 2012; van Nostrum, 2011). Therefore, the focus in this review will be on dendritic core–shell nanocarriers for drug delivery. After the introduction of the general concepts and the history of unimolecular micelles, the review will be divided into chapters according to the nature of the core of the dendritic core–shell nanocarriers. We will describe interesting, conceptual examples based on hydrophilic and hydrophobic cored structures and on core–multishell systems. Further recent literature examples on dendritic core–shell nanocarriers will be given in Table 1.

2. Unimolecular micelles

Amphiphiles can form supramolecular micelles above a critical micelle concentration (cmc). In contrast, unimolecular micelles are single-molecule micelles with a distinct core and shell that are covalently bound together. Supramolecular micelles, which are thermodynamic aggregates, can fall apart due to high dilution or shear forces at concentrations under their cmc. On the other hand, unimolecular micelles are stable regardless of their concentration (Fig. 1), which makes them especially attractive candidates as nanocarriers for drug delivery applications (H. Liu et al., 2000; Hawker et al., 1993; Liu et al., 1999; M. Liu et al., 2000; Moorefield and Newkome, 2003; Newkome et al., 1991; Patri et al., 2002).

Drug delivery with unimolecular micelles can be accomplished in two different ways either by conjugating the drug to the scaffold of the unimolecular micelle or by physically encapsulating the drug within the scaffold of the unimolecular micelle (Fig. 2). For bioimaging or theranostics approaches dyes can be used instead of or additionally to drugs. Conjugation is often performed with cleavable linkers that enable the drug's release. Even though the conjugation approach has been widely employed too, this review will describe the use of unimolecular micelles via encapsulation.

Encapsulation can occur within unimolecular micelles in three different ways. The guest can be encapsulated in the core, in the shell, or at the interface of the core and the shell of unimolecular micelles (Fig. 3a–c). In addition to this, it was found that unimolecular micelles, although they represent single-molecule micelles per se, do not necessarily transport their cargo in a unimolecular fashion. Instead, the encapsulation can occur in a fourth way, whereby the guest is encapsulated within aggregates of several unimolecular micelles (Fig. 3d). The fourth encapsulation mechanism is therefore not unimolecular but supramolecular. Depending upon the mechanism of transport, the size of the nanocarrier could also vary, which is an important factor that needs to be considered for the design of a successful drug delivery system. For instance, transport through supramolecular self-assembly results in larger aggregates. In general, the size of the nanocarriers that transport through unimolecular mechanisms varies from a few nanometers to tens of nanometers depending on the molecular weight of the

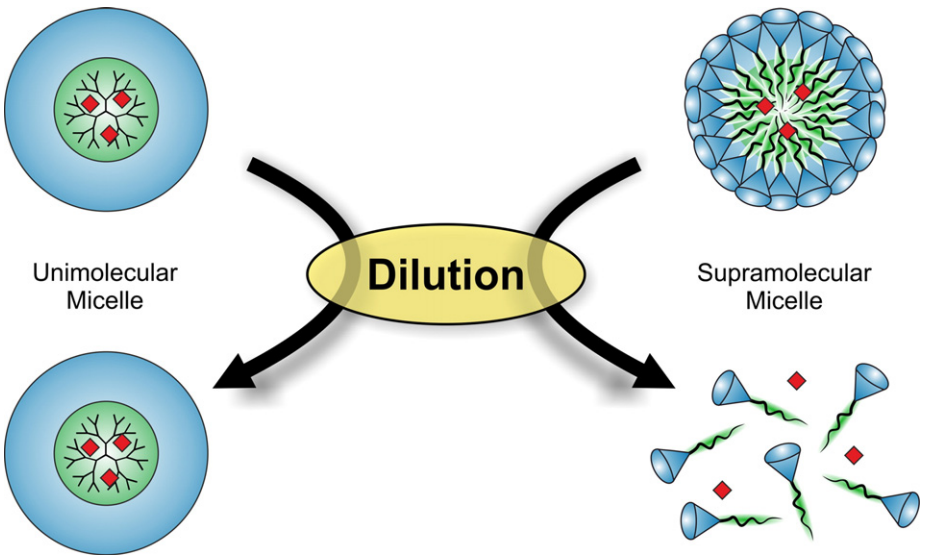

Fig. 1. Different behaviors of unimolecular and supramolecular micelles under dilution. Unimolecular micelles are stable and supramolecular micelles can fall apart.