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Mini review

Dendrimers as a promising tool in ocular therapeutics: Latest advances and perspectives

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ABSTRACT

Dendrimers have called the attention of scientists in the area of drug and gene delivery over the last two decades for their versatility, complexity and multibranching properties. Some strategies for optimizing drug pharmacokinetics and site-specific targeting using dendrimers have been proposed. Among them, those related to treating and managing ocular diseases are of special interest. Ocular therapies suffer from significant disadvantages, including frequent administration, poor penetration and/or rapid elimination. This review provides an overview of the recent and promising progress in the dendrimers field, focusing on both the anterior and posterior segments of the eye ocular targets, the use of dendrimers as a strategy for overcoming obstacles to the traditional treatment of ocular diseases and an outlook on future directions. Finally, a first approach to ocular safety with dendrimers is intended that accounts for the state-of-the-art science to date.

1. Introduction

In ocular drug delivery, most ophthalmic drugs are administrated topically in the form of eye drops. Unfortunately, due to the special anatomic structure and efficient protective physiological mechanisms of the eye, particularly 1) the epithelium (the outermost layer of the cornea), which hampers drug penetration, and 2) lacrimation (induced by standard application of eye drops on the eye surface), which causes dilution of the drug and drainage of the eye drops from the ocular surface (Richichi et al., 2016), the time for drug absorption is reduced to only a few minutes and bioavailability is very low, typically less than 5% (Yao et al., 2010a, 2010b). In order to enhance the ocular bioavailability, many ophthalmic drugs are applied in high concentrations or increased frequency of administration, but these may cause both ocular and systemic side-effects (Wu et al., 2014; Rodriguez Villanueva et al., 2016).

The implementation of effective strategies to increase the drug residence time on the ocular surface, with the aim of minimizing systemic drug side effects and reducing dosing frequency, is one of the main challenges in ocular pharmaceutical technology (Bravo-Osuna et al., 2012). Among them, the use of dendrimers has caught the eye of scientists worldwide. In 1978, Buhleier et al. (1978), and few several years later, in the same sense, Tomalia et al. (Tomalia et al., 1985), firstly described the synthesis of a new type of non-linear-shaped molecules. Dendrimers (Din Greek, dendron = tree and meros = branch) are globular tree-like branched nanostructured polymers (~3–20 nm) (Xu et al., 2013) that can have neutral, negative, or positive functional groups at the terminus of their branches (Kompella et al., 2013). They are composed of a central molecule known as the "core" and side chain moieties known as "dendrons" (Honda et al., 2013) (Fig. 1A). As a result, three main parts can be clearly distinguished: (1) an inner core; (2) highly branched, repeating units called layer of generations; and (3) peripheral multivalent functional groups (Chaplot and Rupenthal, 2014) that can modulate the local environment to enable unique tissue interactions (Kambhampati et al., 2015). Drugs can be either entrapped in the dendrimer network through hydrogen bonds, hydrophobic interactions and ionic interactions or they can be conjugated through covalent bonds (Fig. 1B). Dendrimers can incorporate a lower amount of drugs than other carriers (Honda et al., 2013). The drug-loading capacity of dendrimers as well as the drug release from dendrimers can be controlled by adjusting the physicochemical properties of the dendrons as well as dendrimer generation (Wu et al., 2015). Dendrimers can also differ in size,

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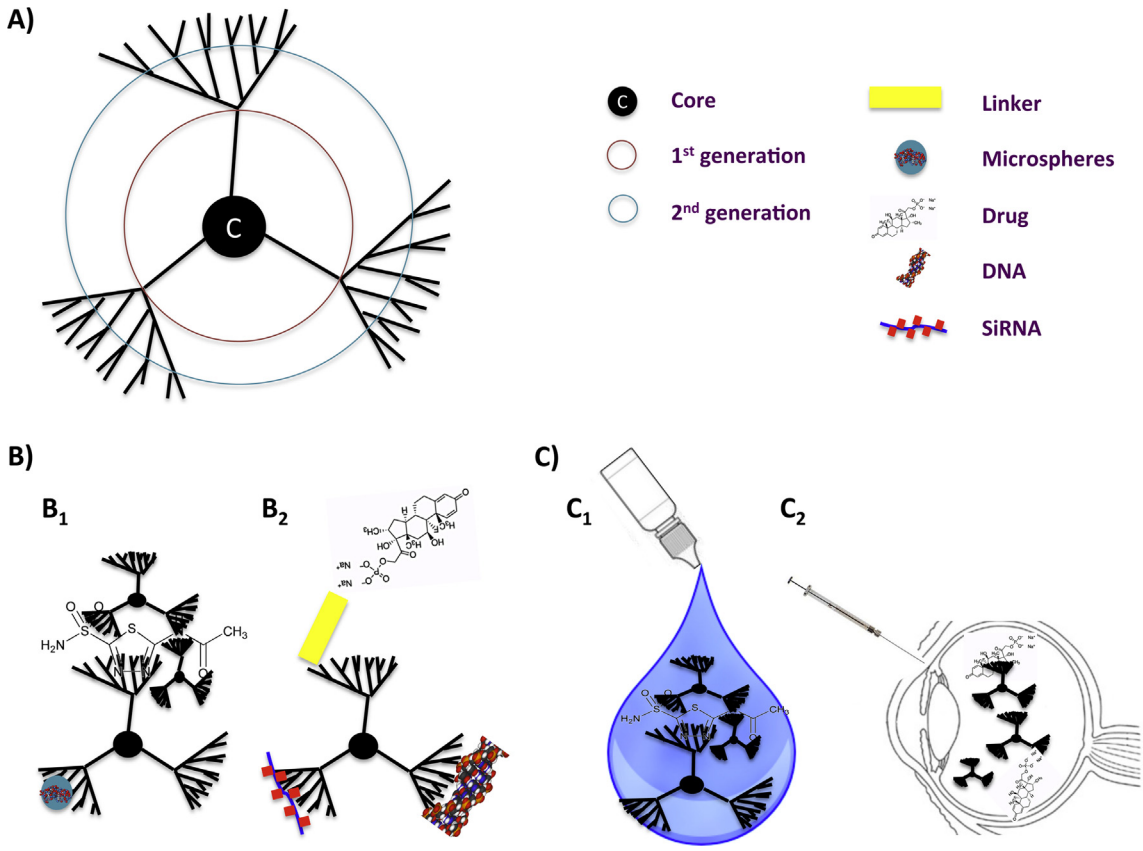

Fig. 1. (A) Schematic representation of dendrimer anatomy and legend. (B) B_1: Dendrimers as vehicles for nano/microspheres and drug encapsulation. B_2: Dendrimers as platforms for conjugation and as vehicles for nucleic acid delivery. (C) C_1: Dendrimers in ocular topical administration. C_2: Dendrimers in intraocular administration.

folding, shape, flexibility/rigidity, architecture and elemental composition (Kannan et al., 2014).

To date, over 100 structurally different dendrimer families have been synthesized. Different dendrimer structures have been explored with the aim of increasing the residence time of drugs on the ocular surface and reducing their systemic absorption and toxicity (Bravo-Osuna et al., 2016) (Fig. 1C_1). Of these, polyamidoamine (PAMAM) has been the most investigated, widely characterized and commercialized dendrimer species for drug and gene delivery (Kompella et al., 2013; Chaplot and Rupenthal, 2014). Their advantages include their water solubility and lack of immunogenicity (Malik et al., 2000; Chaplot and Rupenthal, 2014). However, some PAMAM dendrimers are toxic in cells and animals due to their polycationic character. It has been demonstrated that modifying the amino groups on the periphery of the dendrimer with poly(ethylene glycol) chains reduces its toxicity and increases the biocompatibility of the resulting polymer (Jevprasesphant et al., 2003; Froehlich et al., 2009), among others, in retinal cells (Marano et al., 2005). PAMAM dendrimers with —OH and —COOH terminal groups are non-cytotoxic and are cleared intact through the urine at lower generations (Iezzi et al., 2012). Of course, partially or fully biodegradable species (e.g., polyether, polyether-co-polyester, phosphate, peptide or PLGA-based) are required when dendrimers are designed for the posterior segment of the eye (Fig. 1C_2). To date, little work has been conducted on this field and only a few precursors could be found in the fragmentary scientific literature, although they are undoubtedly a good step in the right direction (Velazquez et al., 2004; Grinstaff, 2007).

This review provides an overview of recent and promising progress in the dendrimer field, focusing on ocular targets (Fig. 2), and the use of dendrimers as a strategy for overcoming obstacles to the treatment of ocular diseases that might improve patient compliance, which is one of the main weak points of chronic therapies at the ophthalmic level.

2. Dendrimers and topical administration

The topical administration of drugs remains the preferred route for treating ocular diseases, primarily because of the ease of application and patient compliance. The eye membranes, such as the cornea, the conjunctiva and the sclera, limit the penetration of drugs to the posterior segment, which hampers the use of topical administration as an effective route of treatment for pathologies affecting the posterior segment of the eye, as only 1–2% of the administered drug reaches the vitreous cavity (Herrero-Vanrell et al., 2014; Souza et al., 2014; Andres-Guerrero et al., 2015). At the moment, they are only prescribed when the focus of treatment is the anterior segment of the eye. If dendrimers are incorporated into formulations, they should demonstrate physicochemical characteristics (pH, osmolality, viscosity) that are compatible with ocular dosage form formulations.

2.1. Drug encapsulation and residence time

The interior of dendrimers is particularly suited for accommodating poorly water- soluble drugs, such as through hydrophobic interactive forces and hydrogen bonding (Rasines et al., 2012; Wu et al., 2015). Dendrimers can accommodate metal salts and nanoparticles as well. Encapsulation increases alongside dendrimer generation and/or the surface chain length (Kojima et al., 2000). Noncovalent drug encapsulation might be the method of choice for solubilizing many bioactive molecules (Kesharwani et al., 2014). One serious concern is the inability of the engineered