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Applications of nanoparticles in ophthalmology

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A B S T R A C T

Nanocarriers, such as nanoparticles, have the capacity to deliver ocular drugs to specific target sites and hold promise to revolutionize the therapy of many eye diseases. Results to date strongly suggest that ocular medicine will benefit enormously from the use of this nanometric scale technology. One of the most important handicaps of the eye as a target organ for drugs is the presence of several barriers that impede direct and systemic drug access to the specific site of action. Superficial barriers include the ocular surface epithelium and the tear film, and internal barriers include the blood–aqueous and blood–retina barriers. Topical application is the preferred route for most drugs, even when the target tissues are at the back part of the eye where intraocular injections are currently the most common route of administration. Direct administration using any of these two routes faces many problems related to drug bioavailability, including side effects and repeated uncomfortable treatments to achieve therapeutic drug levels. In this regard, the advantages of using nanoparticles include improved topical passage of large, poorly water-soluble molecules such as glucocorticoid drugs or cyclosporine for immune-related, vision-threatening diseases. Other large and unstable molecules, such as nucleic acids, delivered using nanoparticles offer promising results for gene transfer therapy in severe retinal diseases. Also, nanoparticle-mediated drug delivery increases the contact time of the administered drug with its target tissue, such as in the case of brimonidine, one of the standard treatments for glaucoma, or corticosteroids used to treat autoimmune uveitis, a severe intraocular inflammatory process. In addition, nanocarriers permit the non-steroidal anti-inflammatory drug indomethacin to reach inner eye structures using the transmucosal route. Finally, nanoparticles allow the possibility of targeted delivery to reach specific types of cancer, such as melanoma, leaving normal cells untouched.

This review summarizes experimental results from our group and others since the beginnings of nanocarrier technology to deliver drugs to different locations in the eye. Also, it explores the future possibilities of nanoparticles not only as drug delivery systems but also as aides for diagnostic purposes.

Contents

Abbreviations: AS-ODNs, Antisense oligonucleotides; CS, Chitosan; CSO, Chitosan oligomers; CsA, Cyclosporine A; ESF, European Science Foundation; HA, Hyaluronic acid; HA-CS NPs, Hyaluronic acid and chitosan-based nanoparticles; HA-PECL NPs, Hyaluronic acid-coated poly-ϵ-caprolactone nanoparticles; IOP, Intraocular pressure; LCS-NPs, Liposome–chitosan nanoparticle complexes; NIH, National Institutes of Health; NPs, Nanoparticles; OIR, Oxygen-induced retinopathy; PBCA, Poly(butyl-cyanoacrylate); PECL, Poly-ϵ-caprolactone; PEG, Polyethyleneglycol; pGFP, plasmid green fluorescent protein; PIBCA, Poly(isobutyl-cyanoacrylate); PLA, Poly-D-lactic acid; PLGA, Poly-D-lactic-co-glycolide; RNAi, RNA interference; rAAV, adeno-associated virus vectors; RPE, Retina pigment epithelium; siRNA, small interfering RNA.

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1. Introduction: what is nanomedicine?

In 2003, the European Science Foundation (ESF) initiated a project aimed at gathering European experts from academia and industry to prepare what was called 'ESF Forward Look on Nanomedicine', published in 2004 (http://www.esf.org/publications/forward-looks.html). Several workshops were conducted to (i) define the field, (ii) discuss the future impact of nanomedicine on healthcare practice and society, (iii) review the state-of-the-art of research, (iv) identify Europe's strengths and weaknesses, and (v) deliver recommendations on research trends and organization. These experts formally defined the field of 'nanomedicine' as "the science and technology of diagnosing, treating and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body". It is noteworthy that this concept is based in complex systems of nanometre-scale size, i.e., from one nanometre to hundreds of nanometres, with the ultimate goal of using them to achieve medical benefits. It is important to bear in mind that the nanometre scale is the scale at which molecules and compounds operate inside living cells.

Soon afterward the ESF's publication, the National Institutes of Health (NIH) in the U.S.A. developed a Nanomedicine Roadmap Initiative (http://nihroadmap.nih.gov/nanomedicine/). As a centrepiece of this initiative, a national network of eight collaborative Nanomedicine Development Centers was established in 2006. That multidisciplinary research initiative was primarily directed towards gathering extensive information about nanoscale intracellular biological structures. That information was to be used in the application of newly developed nanomedical therapies to treat specific diseases. As an example of the interest that this topic has awakened in the vision research community, an education course 'Nanotechnology and Nanomedicine: Applications for Vision Research', was organized in 2005, co-sponsored by the Association for Research in Vision and Ophthalmology and the NIH's National Eye Institute.

As anyone can envision, nanomedicine has a relevant position in the global agenda for future development of medical research in the 21st Century. One of the main topics in nanomedicine research is the pharmaceutical development of drug delivery systems. Its goal is the development of improved nano-sized drug carriers consisting of at least two components, one of which is the active therapeutic ingredient. These drug-loaded carriers can be termed 'nanopharmaceuticals' or 'nanomedicines' in a broad sense. This review will focus on the ocular applications of nanoparticles (NPs), a particular type of these drug delivery systems.

2. Drug delivery systems

Among the different approaches that have been taken to develop more efficient treatments to fight against human and animal life-threatening or debilitating diseases, the development of drug delivery systems is noteworthy. The purpose of a drug delivery system is to act as a carrier or vehicle for an entrapped or bound therapeutic agent to reach precisely and effectively the desired site of action. Here we focus on delivery systems that target ocular structures. This concept is particularly interesting when one takes into account the physicochemical features of the frequently marketed biotechnological macromolecules, such as peptides, protein, antibodies, and nucleic acids (Conti et al., 2000; Degim and Celebi, 2007; Levy-Nissenbaum et al., 2008).

However, a drug delivery system is more than a simple (nano) carrier. All of the science and technology behind the design of drug delivery systems intends to achieve solutions for key aspects of modern treatments: (i) to control the release of the active agent so that a therapeutic concentration is maintained over a prolonged period of time, (ii) to develop organ or site-specific or even disease-specific targeting, and (iii) to provide new or more convenient routes of administration for drugs able to reach those locations in the body that are difficult to access. The ultimate goals are to better manage relevant drug-related parameters, such as pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and to improve therapeutic efficacy (Vanderwoot and Ludwig, 2007; Sahoo et al., 2008).

There are different kinds of drug delivery technologies that are designed to serve as drug delivery systems (Medina et al., 2007; Sahoo et al., 2008; Gaudana et al., 2009). These include, among others, transdermal patches, implants, nanodevices, and cell encapsulation devices. Among nanoparticulate-based drug delivery systems (or nanosystems) (Table 1) one can find different polymeric formulations made of non-degradable polymers and biodegradable polymers that are either hydrophilic or hydrophobic. Examples of nanosystems that differ in composition include the following: (i) Nanoparticles (NPs) consist of 1 μm or smaller particles composed of various polymers or materials. These are described in detail below. (ii) Liposomes are lipidic membranes, similar to plasma membranes, and surround an aqueous core. A variant of liposomes are niosomes, consisting of non-ionic surfactants. (iii) Emulsions consist of stabilised oil-in-water or water-in-oil mixtures. Others include (iv) nanosuspensions, (v) dendrimers, (vi) nanoparticle-loaded contact lenses, (vii) nanotubes and fullerenes composed of carbon-based nanomaterials, and (viii) quantum dots made of semiconductor materials with fluorescent properties and covered with other materials. However, drug delivery systems other than those collectively named as "nanoparticles" are out of the scope of this review, and therefore we will not comment on them.

3. The eye as a target organ for drug delivery systems

There are a plethora of ocular disorders that may be vision-threatening. The responsiveness towards classically developed drugs is limited and most fail to correct the underlying problem. Thus, there is a scarcity of truly curative treatments for most eye diseases. The main reasons for these limitations are biopharmaceutical problems related to the special characteristic of the eye that restricts drug bioavailability. The eye is partially isolated from the remainder of the body by several types of barriers that impede the effective passage of many drugs (Fig. 1), leading to