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Review article

Nanocarriers of nanotechnology in retinal diseases

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Abstract

We are approaching a new era of retinal pharmacotherapy where new drugs are rapidly being worked out for the treatment of posterior-segment disease. Recent development in ocular drug delivery systems research has provided new insights into drug development, and the use of nanoparticles for drug delivery is thus a promising excellent approach for advanced therapy of ocular diseases. The primary goal is to develop a variety of drug delivery systems to complement and further enhance the efficacy of the available new medications. The ideal sustained release technology will provide a high level of safety with continuous release over an extended period of time while maintaining almost total drug bioactivity.
The use of nanocarriers, such as cyclodextrin nanoparticle suspension, liposomes, nanospheres and, nanoemulsions for gene therapy of retinal diseases has been highlighted in this review.

Keywords: Nanotechnology, Intravitreal injection, Drug delivery system, Nanoparticles, Posterior segment eye disease

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Introduction

Nanotechnology involves creation and utilization of materials, devices or systems on the nanometer scale. This field is currently undergoing explosive development on many fronts. The technology is expected to create innovations and play a critical role in various biomedical applications, not only in drug delivery, but also in molecular imaging, biomarkers and biosensors.

The eye is a relatively isolated organ divided into anterior and posterior segments with numerous avascular structures.[1] In this regard, the efficacy of topical drug delivery via eye-drops is only limited to the treatment of anterior segment eye diseases. Drugs can enter the posterior segment of the eye via three distinctive noninvasive routes: (1) through conjunctiva/sclera after topical application; (2) from the cornea and aqueous humor after topical application; and (3) from the systemic circulation after topical, parenteral, oral, or other administration routes that deliver drug to the blood circulation.

The eye, particularly the posterior segment, is composed of tissues that are difficult for drugs to penetrate because of structural peculiarities such as the barrier function. Thus, many research studies on nano-sized drug carriers have been conducted in the field of ophthalmology.[2,3]

In this review, the focus will be on the use of nanocarriers, such as cyclodextrin nanoparticle suspension, liposomes, nanospheres and nanoemulsions, and highlights the use of nanoparticles for gene therapy of retinal diseases.

What is micro and nano scale?

Nanotechnology refers to a field of science whose unifying materials are close to molecular scale on dimensions between 1 and 1000 nm (Fig. 1). The macroscopic classification of ophthalmic dosage forms is not related to their microscopic structure and they cannot per se be defined as micro- or nano-technology such as gel-forming solutions, powders for solutions, ophthalmic suspensions, ophthalmic ointments,

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ophthalmic emulsions (e.g., creams), ophthalmic gels, and ocular inserts.[4]

Micro- and nano-technological drug formulations are classified according to the diameter of their particulates. Microtechnology usually refers to technological devices with dimensions close to 0.1–100 μm (102–105 nm) and particles between 0.1 and 100 μm are called microparticles. Drop size in pharmaceutical emulsions is between 0.1 and 1 μm (102–103 nm). Microemulsions form droplets that are between 5 and 140 nm and, thus, should be more correctly referred to as nanoemulsions. Microparticles can consist of micronized drug particles for intravitreal injection but more often such particles consist of micronized polymer/drug matrix-like structures, i.e., microspheres, or polymer-coated microparticles.

Nanoparticles are particles with at least one dimension less than 100 nm for example, the size of liposomes is frequently between 10 and 1000 nm. Nanoparticles can refer to nanospheres (e.g., drug/polymer matrix) or nanocapsules (e.g., polymer-coated drug particles). Examples of nanoparticles for intravitreal drug delivery include albumin nanoparticles for delivery of ganciclovir and a formivirsen analog,[5] and tamoxifen-loaded nanoparticles.[6] Nanoclusters are nanoparticles formed by molecular aggregation and nanospheres are nanoparticles where the active ingredient is encapsulated.

Structural barriers of the eye

Eye structures that function as a barrier to decrease the permeability of the eye to pharmacological agents include the corneal epithelium and endothelium, the sclerocorneal parenchyma, the inner and outer blood–retinal barriers, and the retinal inner limiting membrane.[7]

Drugs penetrate the epithelium either transcellularly or paracellularly. The transcellular route predominates for lipophilic drug molecules whereas the paracellular route predominates for hydrophilic molecules and small ions. The pore size has been estimated to be about 1 nm (permeable for drugs with molecular weight (MW) less than about 700 Dalton) although studies have indicated that some pores could be up to 5 nm in diameter.[8,9] It is accepted that most drugs permeate the epithelium via passive diffusion and, although drug transporters have been located in the epithelium, their significance is still unclear.[10] As a result, less than 5% of the drug can cross the corneal barrier and gain access to the inner eye.[11–13]

The endothelium is a membrane one cell layer with large intracellular junctions. It can be considered as a leaky lipophilic barrier that offers no permeation resistance toward hydrophilic drugs but may offer some resistance toward lipophilic drugs.[14] Conjunctiva is approximately 15–25 times more permeable than the sclera and the sclera is

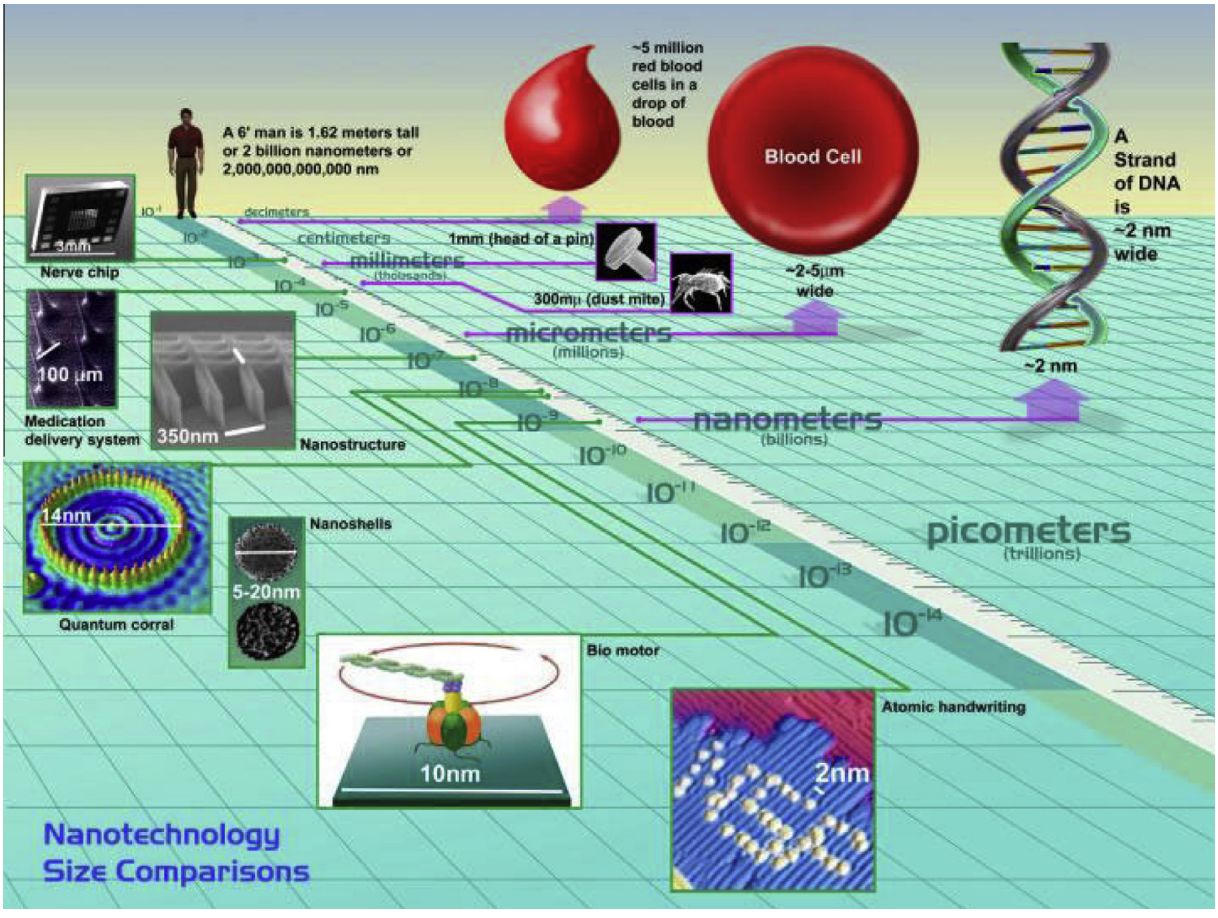

Figure 1. Nano scale (This picture is from http://www.tzhealth.com/health/Nanometer/2007-10-17/15240.html).