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# Nanotherapy for posterior eye diseases

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Fluorescein isothiocyanate-dextran
Polyethyleneimine
Bevacizumab
Ranibizumab
Verteporfin (PubChem CID: 5362420)
Rostaporfin (PubChem CID: 23725012)
Methoxypoly(ethylene glycol)-poly (β-caprolactone)
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ABSTRACT

It is assumed that more than 50% of the most enfeebling ocular diseases have their origin in the posterior segment. Furthermore, most of these diseases lead to partial or complete blindness, if left untreated. After cancer, blindness is the second most dreaded disease world over. However, treatment of posterior eye diseases is more challenging than the anterior segment ailments due to a series of anatomical barriers and physiological constraints confronted for delivery to this segment. In this regard, nanostructured drug delivery systems are proposed to defy ocular barriers, target retina, and act as permeation enhancers in addition to providing a controlled release. Since an important step towards developing effective treatment strategies is to understand the course or a route a drug molecule needs to follow to reach the target site, the first part of the present review discusses various pathways available for effective delivery to and clearance from the posterior eye. Promise held by nanocarrier systems, viz. liposomes, nanoparticles, and nanoemulsion, for effective delivery and selective targeting is also discussed with illustrative examples, tables, and flowcharts. However, the applicability of these nanocarrier systems as self-administration ocular drops is still an unrealized dream which is in itself a huge technological challenge.



## 1. Introduction

Diseases affecting posterior eye segment are presently increasing at an alarming rate. These include age-related macular degeneration (AMD), diabetic macular edema, viral retinitis, proliferative vitreoretinopathy, posterior uveitis, retinal vascular occlusions, choroid neovascularization (CNV), and diabetic retinopathy, to name a few. Most of these diseases may invariably lead to permanent vision loss if left untreated [1]. Of the total debilitating ocular diseases, 55% are posterior segment diseases, while ophthalmic pharmaceutical sales (in the year 2007), accounting for the posterior segment ailments, was only 5% of the total sale of ocular products. The most common, present-day treatment option for posterior segment ocular disorders is surgery. However, with a better understanding of the anatomy of the eye, the pathophysiology of these posterior eye diseases, and the advancement in ocular delivery systems and techniques, several effective novel drug therapies are now being offered as the viable alternatives [2].

The treatment of these diseases requires a direct and local application of the agent to the posterior eye segment at a therapeutic concentration because the delivery of exogenous molecules to the intraocular tissues including the retina is significantly limited [3], especially via the topical and systemic routes. The eye is a highly protected organ with several anatomical and physiological barriers in place, viz. the cornea and conjunctiva, the blood–aqueous barrier, and the blood–retinal barrier. However, the use of nanostructured delivery systems have been shown to defy these barriers and target internal eye tissues, including retina, even following topical application. Present review endeavors to include a variety of such studies in which nanocarrier systems have been developed to overwhelm limited bioactivity and bioavailability of therapeutics to retina and other posterior eye tissues. Although most of these studies are in a preclinical stage, but the excitement associated with the promise, such an option holds, makes it highly appropriate to review these studies and explore the plethora of possibilities offered therein.

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## 2. Routes for Posterior Delivery

The commonly available routes (Fig. 1) to target posterior segment of the eye are topical, systemic, intravitreal, and periocular, which are discussed below in brief. Table 1 highlights the various aspects of these routes along with advantages and disadvantages associated with each route.

### 2.1. Topical Delivery

Topical delivery is a relatively easy and a less risky method of drug administration. However, delivery to the posterior segment via this route is considered inefficient and unsuccessful, as <5% of the topically applied dose enters the eye and a fraction of it (0.001%) is expected to reach the posterior segment [4].

This is attributed to a variety of reasons: (i) limited volume of administration (30 μL); (ii) fast clearance from ocular surface; (iii) metabolism of the active by tear enzymes; (iv) nonproductive uptake into systemic circulation via highly vascularized conjunctiva, choroid, uveal tract and inner retina [5–7]; (v) anterior membrane barriers (cornea, conjunctiva, and sclera); (vi) aqueous humor outflow; (vii) long diffusional path [8]; and (viii) acellular nature of the vitreous, which may negatively impact the pharmacokinetics and distribution of topically applied drugs [9].

### 2.2. Intravitreal Delivery

Intravitreal administration involves the direct administration of drug solution/suspension into vitreous humor *via* pars plana using a 30-G needle [10]. In contrast to the topical and systemic routes, intravitreal injection makes high concentrations of drug locally available to the internal eye tissue, including the choroid and the retina. Inoue et al. [11] compared sub-Tenon and intravitreal injection of triamcinolone acetonide and found that the concentration of triamcinolone acetonide available in the vitreous humor was more when applied intravitreally. Similarly, the intravitreal administration of Macugen® (pegaptanib sodium; Pfizer) and Lucentis® (ranibizumab; Genentech/Novartis), the vascular endothelial growth factor (VEGF) inhibitors, is highly successful for the control of AMD.

Agents with molecular weight less than 500 Da when applied intravitreally, however, tend to be drained off from the site of application with a half-life of less than 3 days, indicating a need for repetitive injections. However, the period requiring a repeat dose may extend from a few days to several months for macromolecular antibodies. For example, the mean number of injections of bevacizumab (Avastin®; Roche) required to be administered per year for the treatment of AMD is three. On the other hand, the recommended dosing frequency of Ranibizumab (Lucentis®) is once a month (0.5 mg; 50 μL) for a minimum of 9 months [12], while Macugen® needs to be injected intravitreally at 6-week intervals for at least one year [13].

Nevertheless, repetitive intravitreal injections, even if spaced widely, are invariably associated with complications, such as vitreous hemorrhage, retinal detachment, cataract, and endophthalmitis. The rate of endophthalmitis and retinal detachment being observed with intravitreal injection is 0.2% and 0.05%, respectively [2]. Moreover, patient compliance is lower with such regimens because of the painful and invasive procedures requiring hospitalization and specially trained physician for administration adding to the cost, in addition to the high cost of the medicine per se.

### 2.3. Periocular Delivery

Periocular route refers to the administration of drug to the region surrounding the eye and includes subconjunctival, peribulbur, posterior juxtascleral, sub-Tenon, and retrobulbar injections. The permeation of radiolabeled mannitol following subconjunctival injection to rabbits indicated direct penetration through sclera as the primary pathway for the delivery of materials to the posterior segment, followed by systemic recirculation and a minor transcorneal uptake [14–16] (Fig. 1).

Periocular route, although not as efficient as the intravitreal route, offers an advantage of lesser invasiveness. A better retinal and vitreal drug bioavailability (about 0.01–0.1%) is achieved via this route in comparison to the topical route of application (about 0.001% or less) [17,18]. Repetitive periocular administration under local anesthesia is possible without direct interference with the vision. Volumes as high as 500–5000 μl of drug solution can be administered via periocular route in humans [19] versus only 50–100 μl being administrable, via intravitreal route.

Evidence suggests that drug concentrations in the ocular tissue are higher following periocular routes of administration compared to intravenous, topical, and oral administrations [9,20].

### 2.4. Systemic Delivery

The availability of drug in the posterior eye segment following systemic administration as tablets, capsules, or intravenous injections is limited by the presence of the blood retinal barrier (BRB), which is selectively permeable to highly lipophilic molecules. Lipid-soluble drugs such as chloramphenicol and minocycline penetrate the BRB, while aminoglycosides (amikacin) and β-lactams (cefazolin) being

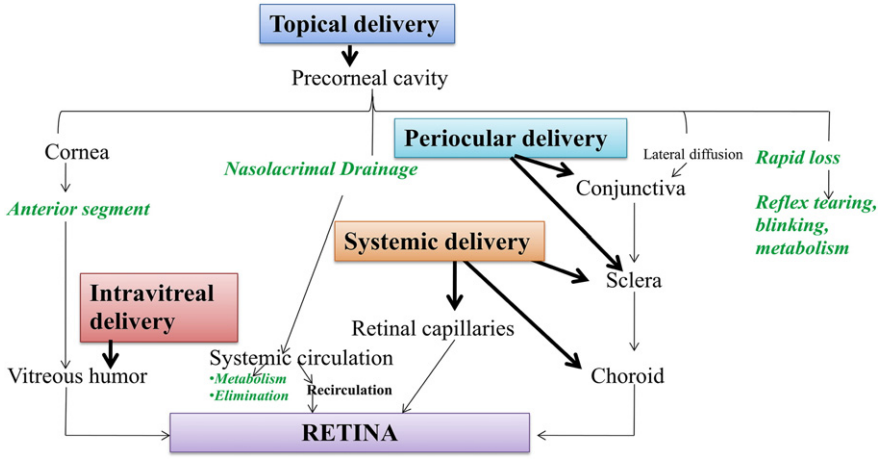


**Fig. 1.** Pathways for distribution of drug to the retinal tissue of the eye following different delivery routes. Italicization indicates nonproductive drug losses.