**22SSUPPLEMENTARY MATERIALS:**

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| --- | --- | --- | --- | --- |
| **ROUTES** | **BARRIERS** | **LIMITATIONS** | **ADVANTAGES** | **REFERENCES** |
| Topical | * Membrane barriers * Elimination pathways on eye surface * Cornea structural complexity * Blood retinal barrier * Aqueous humor flow gradient * Tight junctions * Tear flow (opposite convective flow ) * Dynamic barriers related to tissue vasculature and clearance by lymphatics | * High frequency of instillations * Nasolacrimal drainage * Restricted volume of application * Blurriness of vision * Pre corneal drug loss * Blinking reflexes | * Non invasive * Patient compliant * Self administrable | [21] |
| Systemic | * Choroidal efflux transporter * Blood Retinal barrier(more selective to highly lipophillic drug) | * High dose administered to achieve the therapeutic concentration. * Unintended adverse effects due to undesirable exposure non targeted areas. * Efflux transporters limit the absorption to the ocular tissues. * Invasive (sometimes) | * Prevent the damage to ocular tissues due to multiple injections. | [22] |
| Periocular  (subconjunctival, subtenon, peribulbar, posterior juxtascleral and retrobulbar  injections) | * Scleral width and thickness * Choroidal vascularisation * Blood retinal barrier | * Drug loses via the episcleral, conjunctival, lymphatic flow * Invasive * Damage to the ocular tissues | * Utilizes the trans-scleral pathway to deliver drugs | [23] |
| Intravitreal | * Blood retinal barrier * Transient diffusion of large molecules is hindered by the layers of vitreal body which act as a semi permeable membrane. * The physical membrane barriers of retina such as retinal pigment epithelium (RPE) | * Invasive * Various side effects such as Glaucoma, cataract, retinal detachment, haemorrhage, degradation of specialised rods and cones  and bacterial endophthalmitis | * Highest bioavailability to the vitreo-retinal-choroidal tissue due to the immense potential to circumnavigate back of the ocular tissue barriers. | [24] |
| Suprachoroidal | * Choroidal vascularisation | * Post operative inflammation and choroidal haemorrhage * Invasive | * Effective therapeutic concentration reaches vitreous humor and choroid. * An important trans scleral innate route for those bioactives which is administered to the scleral layer. |  |

**Supplementary Table 1: Posterior Segment Delivery Routes and Barriers**

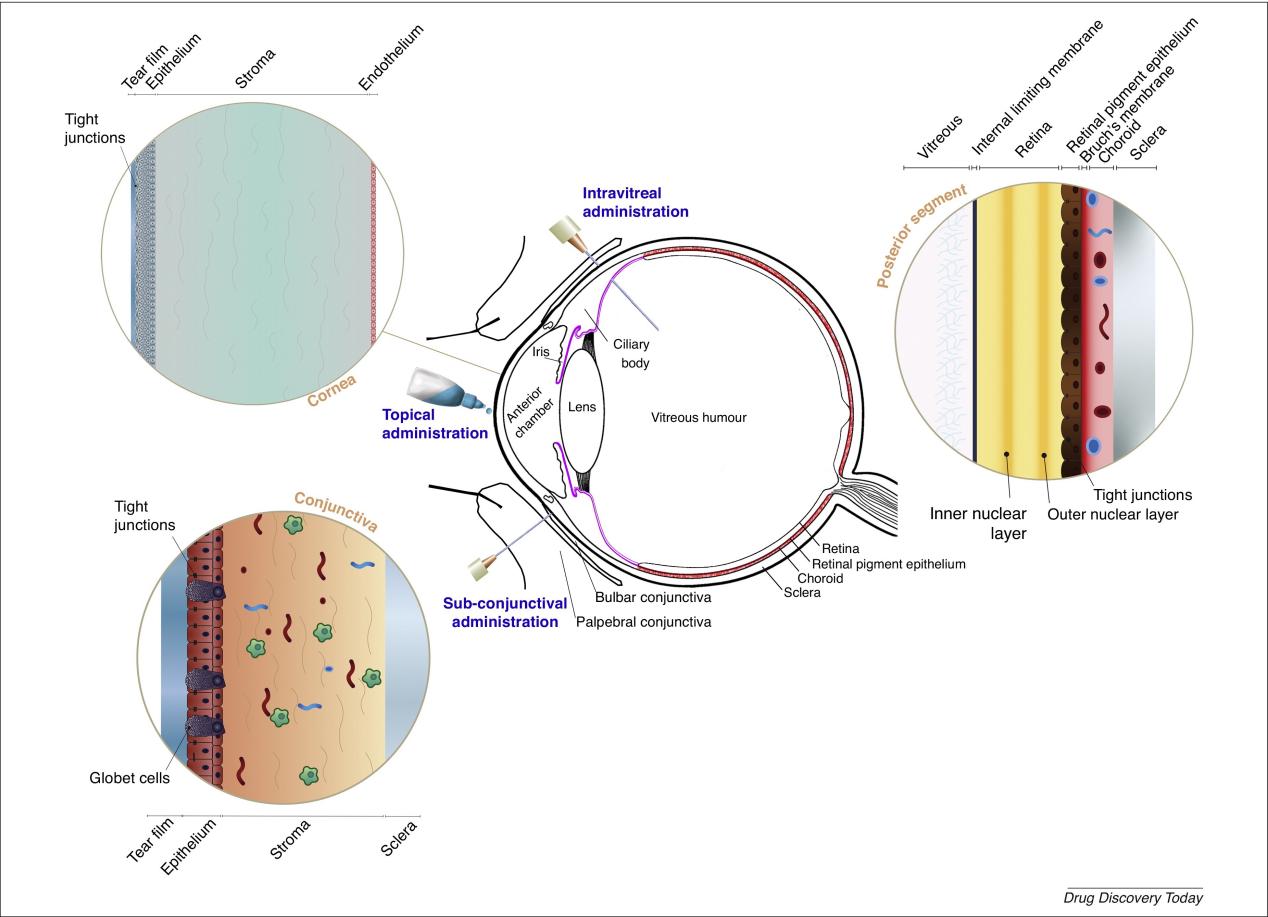
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| **Disease** | **Classification** | **Signs and symptoms** | **Treatment** | **References** |
| AMD (Age related macular degeneration) | Non-exudative- Dry AMD | Break down of photoreceptors, retinal pigment epithelium (RPE) and choriocapillaries | Administration of specialized high dose of antioxidants, zinc and vitamin supplements | [26] |
| Exudative -Wet AMD | Growth of abnormal blood vessels behind the retina, macula, disruption of Bruch’s membrane and degeneration of RPE leading to complete loss of vision | * Intravitreal injection of anti-VEGF agents like ranibizumab, pegaptanib sodium and bevacizumab * Inj. Pegcetacoplan   Approved by FDA on February 17, 2023). | [27,28] |
| DME (Diabetic macular edema) | Focal or non-cystoid DME | Small aberrations in retinal blood vessels followed by intra-retinal leakage | With the aid of Corticosteroids and Focal or grid laser therapy | [29] |
| Diffuse or cystoids DME | Formation of microcrysts and dilation of retinal capillaries | NSAIDs, Corticosteroids, Carbonic Anhydrase Inhibitors, Anti VEGF agents | [30] |
| PVR (Proliferative vitreoretinopathy) | Based on the inflammation of retina: focal, diffuse, subretinal, circumferential  Based on the location of scar tissue: anterior, posterior | Simple scar formation and proliferation of cells in vitreous and retina | Vitrectomy, Intravitreal methotrexate | [31] |
| Uveitis | Anterior uveitis, intermediate uveitis, posterior uveitis,   pan-uveitic uveitis | Inflammation occurs in the middle layer of eye (uvea) | Corticosteroids and immunosuppressive agents | [32] |
| CMV (Cytomegalo virus retinitis) |  | Inflammation of the retina, retinal detachment and complete blindness | Cidofovir, ganciclovir (GCV) and foscarnet | [33] |
| Diabetic Retinopathy | Blurred Vision | Chronic hyperglycemia renders damage to retinal blood vessels,with consequential vasculatr abomral leakages and cell death, thereby swelling. | * Laser photocoagulation * Anti-VEGF medications * Steroid injections * Laser Therapy | [34] |
| Floaters in visual field | Bleeding in th vitreous humor due to the aforementioned damage and rapid formation of new blood vessels. |
| Development of blind spots | Damage to retinal blood vessels |

**Supplementary Table 2: Classification of PSEDs with their symptoms and treatment.**

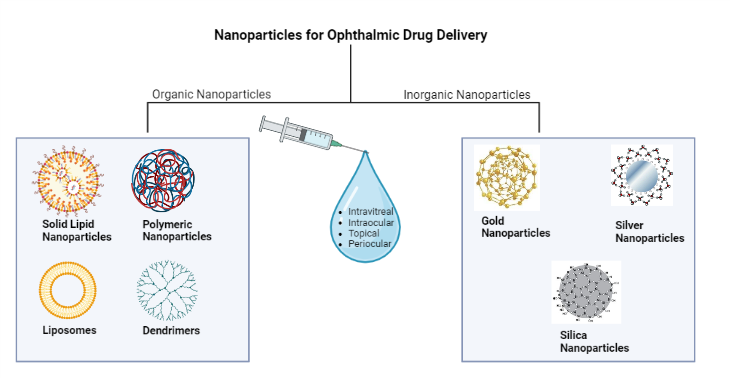
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| --- | --- | --- |
| **Drug binding to tear proteins** | * Reduces the ocular bioavailability * Tear protein – 0.7% of total protein * Protein and efflux transporters | [54] |
| **Systemic drug absorption** | * Nasolacrimal drainage * Non productive | [55] |
| **Corneal Factors** | Corneal layers- six layered   * Lipophilic Dua’s layer * Hydrophilic stroma * Endothelium (innermost)- selective permeability, facilitated diffusion, secretary role, maintenance of corneal transparency | [56] |
| **Melanin binding** | Drugs binding to melanin   * Ephedrine * Timolol | [57] |
| **Pre corneal drug loss** | * Volume of the instillation * pH and partition co efficient * Tonicity * BCS class of drug * Viscosity of the formulation | [58] |
| **Metabolic parameters** | Enzymes involved   * Aldo/ ketone reductase * Cyclooxygenase * Monoamine oxidase * Transferase * Hydrolase * Aldehyde oxidase * Cytochrome P450 | [59] |

**Supplemetary Table 3: Factors affecting intraocular bioavailability.**

**Supplementary Figures:**

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**Supplementary Figure 1: Conjunctival barriers with respect to their topical administration and topical administration. Reproduced with permission from [20]. Copyright, Elsevier.**



**Supplementary Figure 2: Novel nanoformulations for the treatment of PSEDs**