Chapter 1
Background of Ocular Drug Delivery

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Abstract Delivery of drugs to the eye is one of the challenges facing clinicians due to the unique anatomy, physiology, and biochemistry of the eye. Current treatment protocols for administration of drugs in eye diseases are primarily solution, gels or ointments. However, these modes of delivery have several drawbacks such as short residence time, short duration of action, the need for repeated administrations and non-specific toxicity. This chapter will introduce a brief discussion on various topics and issues relevant to ocular therapeutics and drug delivery.

Keywords Ocular · Eye · Drug delivery · Formulations

Introduction

The eye is a highly complex organ with a unique anatomy and physiology that protects it and even makes drug delivery to the eye a major challenge to formulation scientists. The eye is divided into anterior and posterior segments (Chap. 2 of this book discusses the detailed anatomy of the eye). Glaucoma, conjunctivitis, blepharitis and cataract are some of the diseases that affect the anterior segment of the eye, while age-related macular degeneration (AMD) and diabetic retinopathy affect the posterior segment. The topical route is the most convenient and patient compliant form of administering drugs to the anterior segment of the eye. Eye drops

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accounts for about 90 % of drugs administered through this route, less than 5 % of the drug administered gets absorbed due to washing off of drugs by tear dilution, reflex blinking, nasolachrymal drainage and other ocular barriers (static and dynamic) in the eye (Gaudana et al. 2010a; Patel et al. 2013). Due to the problems mentioned above, administration of drugs to the posterior segment of the eye using the conventional eye drop does not achieve therapeutic drug concentration.

Intravitreal and periocular routes are recommended for delivery of drugs to the posterior segment of the eye. These routes have their own limitations: repeated injections through intravitreal route is painful, thus reducing patient compliance. In periocular route, there is ease of administration but the static and dynamic barriers constitutes a problem.

In view of all these, novel formulations have been investigated for the delivery of drugs especially to the posterior segment of the eye to overcome the ocular barriers. Some of these formulations include: sols, liposomes, dendrimers, microparticles, nanoparticles, nanomicelles, implants, contact lenses, microneedles and in situ thermosensitive gels.

Ocular Barriers

There are two major barriers in the eye: blood-aqueous barrier (BAB) and blood-retina barrier (BRB).

BAB consists of the endothelium of the iris/ciliary blood vessels and the non-pigmented ciliary epithelium, both located in the anterior segment of the eye. These cells form tight junctions of the "leaky" type. BRB consists of two types of cells viz retinal capillary endothelia cells (inner BRB) and retinal pigment epithelium cells (RPE) (outer BRB). Both have tight junctions of the "non-leaky" type thus restricting movement of drugs into the retina. This explains why after systemic administration of drugs, the therapeutic level is hardly achieved in the retina (Gaudana et al. 2010b; Occhiutto et al. 2012). These barriers are discussed in detail in Chap. 3 of this book.

Drug Delivery to the Eye

The division of the eye into anterior and posterior segment is actually adapted for the ocular delivery of drug since the method and route of administration of a drug is dependent on the part of the eye segment (Cohen 2012).

Topical instillations are efficient when delivering drugs to the anterior segment of the eye. Despite the relatively small proportion of administered drug dose that reaches the tissues in the anterior segment of the eye, topical instillation still remains effective because of the high concentrations of drug administered (Geroski and Edelhauser 2000). Preservatives such as benzalkonium chloride present in eye

drops have been shown to act as permeability enhancers thus improving the penetration of drugs into ocular tissues (Chen et al. 2011). For years, delivery of therapeutic doses to the posterior segment tissues posed a significant challenge to ophthalmologists. Systemic, intraocular and periocular routes were been used but the challenges posed by the ocular barriers were not allowing therapeutic doses to be delivered to the targeted tissues.

In the early 2000s, liposomal verteporfin was injected systemically coupled to laser infrared therapy to close abnormal choroidal neovessels complicating AMD (Wormald et al. 2005; Cohen 2012). A few years later, anti-vascular epithelia growth factor (anti-VEGF) was developed for the treatment of wet AMD using repeated intravitreous injections (Vedula and Kryzstolik 2008), thus marking the beginning of a new era for delivery of drugs into ocular tissues.

New Trends in Ocular Drug Delivery

Prodrug Design

Prodrugs, developed about six decades ago, are derivatives of drug molecules that are chemically or enzymatically transformed in vivo into the active parent drug (Stella and Himmelstein 1980). Prodrugs are designed to improve solubility, stability, bioavailability and also to decrease side effects of ophthalmic drugs. For successful utilization of prodrugs, recognition of drug properties and participation of barriers at target site are critical factors. Prodrugs are useful for improving drug permeation by enhancing lipophilicity and by modulating aqueous solubility. Different approaches are used:

Functional Group Prodrug Approach Ester prodrugs are derived from carboxylic or hydroxyl functional groups. These functional groups exist in ionized form in physiological condition thereby limiting the passage of drug through the lipid membrane leading to reduced bioavailability. The first ophthalmic prodrug to be produced was dipivefrine, an ester prodrug of epinephrine to decrease intraocular pressure (Hussain and Truelove 1976; Jarvinen and Jarvinen 1996). Corneal penetration with dipivefrine was 10 times better than epinephrine (Wei et al. 1978; Mandell et al. 1978).

Transporter Target Prodrug Approach Prodrugs are synthesized in such a way that they will have an affinity for influx transporters, which sees them as substrates and thus transports them across the membrane. Examples of transporters used in ocular delivery include peptides (Anand et al. 2003; Janoria et al. 2010), amino acids (Balakrishnan 2002; Katragadda 2008) and in recent times vitamins such as biotin (Janoria et al. 2009) and vitamin C (Dalpiaz 2005) are being used.

Lipid Prodrug This approach was designed to improve lipophilicity of hydrophilic drugs molecules hence increasing corneal permeability. The drug molecule is

covalently bound to a lipid moiety such as diglyceride or phosphoglyceride, fatty acids. Lipid prodrugs diffuse across a cell membrane by facilitated diffusion thereby resulting in improved cellular absorption. If the drug is too lipophilic, permeability will be limited.

Dendrimers

They are macromolecular "tree-like" nanostructured polymer with several reactive end group that forms an internal core. The unique structure makes them solubilize poorly water-soluble drugs (Cheng et al. 2008) and also mimic globular proteins (Esfand and Tomalia 2001; Hecht and Frechet 2001). Dendrimers have been reported to enhance corneal residence time of topically administered drugs (Yang et al. 2012), target neuroinflammation in retinal degeneration (Iezzi et al. 2012), used as sutures upon removal of cataract (Wathier et al. 2004).

Liposomes

They are vesicular systems comprising of an aqueous inner core and an outer layer made up of phospholipid bilayers from a natural or synthetic origin. They are classified based on lipid bilayer and sizes such as SUVs (small unilamellar vesicle), MLV (multilamellar vesicle), LUV (large unilamellar vesicle) and GUV (giant unilamellar vesicle). Liposomes can be used to deliver both hydrophilic and hydrophobic drugs to the eye, which is one of the advantages apart from being biocompatible and non-toxic (Schwendener 2007; Mishra et al. 2011). However, liposomes have limitations such as stability, sterilization, and low encapsulation efficiency. They can become chemically unstable due to hydrolysis or oxidation of their unsaturated lipids or physically unstable due to leakage of drugs which could lead to aggregation (Agarwal et al. 2016). Rathode and Deshpande suggested that the stability problems might be overcome by lyophilization (Rathode and Deshpande 2010). Coating of liposomes with high molecular weight chitosan has been shown to reduce aggregation, increase viscosity thus improving residence time in the cornea (Mehanna et al. 2010).

Nanomicelles

They are self-assembled colloidal structures in the size range of about 10–100 μm consisting of an inner hydrophobic core and an outer hydrophilic shell (Trivedi and Kompella 2010). Nanomicelles are divided into three categories: Polymeric, Surfactants and Polyionic complex micelles (PIC). Surfactant micelles have high

critical micelle concentration (CMC) and are unstable in solution whereas, polymeric micelles have low CMC and are stable on dilution (Vaishya et al. 2014). PIC are water soluble with a charged core-forming block. The driving force for micelle formation is the electrostatic charge interaction between this block and the oppositely charged drug stabilizes the micelle. Selection of carrier depends on the physicochemical properties of the drug, site of action, the interaction between drug and carrier and biocompatibility (Vaishya et al. 2014). The shape and size of surfactant micelles depend on the concentration of surfactants, pH, temperature and the ionic strength of the surfactant. Nanomicelles have the following advantages: minimal drug degradation, easy permeation through the ocular epithelium, enhanced bioavailability and no irritation (Cholkar et al. 2012).

Implants

They are polymeric devices inserted into the eye surgically, to prolong the release of a drug in the eye. Polymers used could be biodegradable or non-biodegradable. The non-biodegradable polymers include polyvinyl alcohol (PVA), ethylene vinyl acetate etc. have been used for sustained release of implants such as Retisert®, I-vation® and IIuvien®. The problem with them is that after the drug has been depleted, the polymer carrier remains in the eye and it needs to be removed surgically and this can lead to non-compliance. If left in the eye, accumulation could lead to other problems like cataract, hemorrhage, retinal detachment and other complications.

The biodegradable polymers that have been used in ocular drug delivery include but not limited to poly lactide-co-glycolide acid (PLGA) and Polylactic acid (PLA). These polymers degrade in the eye when the drug has been depleted leaving no residue. Examples of implants using biodegradable polymers are Ozurdex® and Surodex® (Haghjou et al. 2011).

Contact Lens

They are curved shaped discs prepared from silicon containing hydrogels or polyvinyl alcohol hydrogels inserted into the eye to cover the cornea. It is separated from the cornea by a thin fluid layer called the postlens tear film. The postlens tear film allows drugs released from the lens to have a residence time of at least 30 min in front of the cornea since the fluid in tear film does not mix readily with a tear in the eye (Creech et al. 2001). Drug bioavailability was increased from less than 5 % in eye drops to about 50 % in contact lenses.

In an experiment conducted by Guzman-Aranguez et al. (2012), they loaded drugs into the lenses by soaking in drug solutions. However this method has its limitations: adequate drug was not loaded and also the drug loaded was released within a few hours. Thus, soaked contact lenses cannot provide slow extended drug release.

Nanoparticles, microparticles, and liposomes can also be loaded on matrix of contact lens to deliver drug to the eye (Gulsen and Chauhan 2004, 2005)

Another method is known as molecular imprinting. The drug (acting as a template) is added before the polymerization of the polymer units. The monomers will arrange as a function of their ability to interact with drug molecules. After polymerization, the drug molecule is removed. This imprinting makes it easier to load more drugs and also to extend the release of the drug (Hirantani et al. 2005; Alvarez-Lorenzo et al. 2006; Tieppo et al. 2012).

The supercritical solvent method is another way of loading drugs onto contact lenses. The drug is dissolved in a high volatile fluid such as carbon dioxide which is brought near the matrix to load the drug (Braga et al. 2012).

Microneedle

They are individual minute needles or array of micrometer-sized needles that are manufactured by adapting the tools of the microelectronics industry (Jiang et al. 2007). They were originally developed for transdermal drug delivery. Microneedles which are solid or hollow were made from stainless sheet metals (Jiang et al. 2007) while glass microneedles were made from borosilicate micropipette tubes (Cho and Olsen 2013). Drugs coated on microneedles were delivered in a minimally invasive manner via interscleral and intracorneal routes (Jiang et al. 2007).

Fenestrated microneedles were developed by Khandan and co-workers and they found that more drugs could be loaded onto this microneedle. These fenestrated microneedles can also be used to load nanoparticles and microparticles (Khandan et al. 2015).

In Situ Thermosensitive Gels

They are polymeric aqueous solutions that change from a sol to gel in response to temperature changes. An example of polymer in this group is poloxamer. Polymers that are thermosensitive behaves as liquid below its low critical solution temperature (LCST). When environmental temperature reaches LCST or above, it forms a gel (Cao et al. 2007).

In situ thermosensitive gels have been shown to increase residence time and also to control release of drugs in the eye (Sultana et al. 2003).

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