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Review Article

ANTI-GLAUCOMATIC NIOSOMAL SYSTEM: RECENT TREND IN OCULAR DRUG DELIVERY RESEARCH

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ABSTRACT

Glaucoma is a disease and characterized by an intraocular pressure higher than the eye can tolerate. The chronic glaucoma with open angle creates a major problem of public health and it is the second leading cause of blindness in the world. Because of the constraints of physiological factors such as lachrymal drainage, lower *cul-de-sac* volume, reflex tearing, drug spillage, and lower corneal permeability onto the cheek; the ocular bioavailability of conventional ophthalmic preparations is very poor. Conventional preparations require frequent instillation, and long term use of such preparations can cause ocular surface disorders. In recent years, significant efforts have been directed towards the development of new carrier systems for ocular drug delivery. Among these, non-ionic surfactant vesicles *i.e.* niosomes could be a potential one for the effective treatment of glaucoma patients and have gained popularity in ocular drug delivery research. This article reviews the constraints of conventional ocular therapy, complications of glaucoma therapy, and newer advances in the field of anti-glaucomatic niosomal formulation.

Keywords: Niosomes, Glaucoma, Ocular delivery, Eye drops.

INTRODUCTION

Eye is the most important and sensitive organ; in fact, it is the window of our soul. The eye is unique organ from anatomical and physiological point of view. The eye has special attributes that allows local drug delivery and non-invasive clinical assessment of disease but also makes understanding disease pathogenesis and ophthalmic drug delivery challenges[1]. In most cases, ocular therapy requires administration of drugs into the cul-de-sac[2]. Because many parts of the eye are relatively inaccessible to systemically administered drugs, the drugs may require delivery to treat the precorneal region for such infections as conjunctivitis and blepharitis, or to provide intra-ocular treatment *via* the cornea for diseases such as glaucoma and uveitis[3]. Similarly, interior segment of eye generally suffers from keratitis, iritis, cataract and glaucoma; however diabetic retinopathy, viral and bacterial infections, malignancies, proliferative vitreal disorders as well as macular degeneration occur generally in anterior portion[4]. The most convenient way of delivering drugs to the eye is in the form of eye drops. But the preparation when instilled into the cul-de-sac is rapidly drained away from the ocular cavity due to tear flow and lachrymal nasal drainage. Only a small amount is available for its therapeutic effect resulting in frequent dosing[5,6]. Cul-de-sac of the eye (the corners) normally holds 7-9 µl of tear but can retain up to 20 to 30 µl if care is taken not to blink[1]. But the volume of drops is approximately 50 µl. This also leads to rapid tear secretion deviating from its normal flow rate of 1 µl/min, and causes subsequent drainage of eye drops. Due to the resulting elimination rate, the precorneal half life of drugs following application of these pharmaceutical formulations is considered to be between about 1-3 min. As a consequence, only the very small amount of about l-3% of the dosage actually penetrates through the cornea and is able to reach intraocular tissues[7]. In addition, the ocular residence time of conventional eye drops is limited to a few minutes due to lacrimation and blinking[8]; and the ocular absorption of a topically applied drug is reduced to approximately l-10%[9]. The drug is mainly absorbed systemically *via* conjunctiva and nasal mucosa[10], which may result in some undesirable side effects[11].

Even, ointment formulation does not minimize the repeated dosing significantly[2]. Still these conventional ocular dosage forms cover nearly 90% of currently available marketed formulation[12]. To overcome these problems, different approaches such as *in situ* forming gel (Abraham et al. 2009)[13], micro- and nanocarrier systems[14, 15], Inserts[16], and vesicular systems[17] have been adopted.

In recent years, vesicles have become the vehicle of choice in ocular drug delivery. Vesicular systems not only help in providing prolonged and controlled action at the corneal surface but also help in providing controlled ocular delivery by preventing the metabolism of the drug from the enzymes present at the tear/corneal epithelial surface[13]. Moreover, vesicles offer a promising avenue to fulfill the need for an ophthalmic drug delivery system that has the convenience of a drop, but will localize and maintain drug activity at its site of action[13]. From a technical point of view, nonionic surfactant vescicles (niosomes) are promising drug carriers as they possess greater stability and lack of many disadvantages associated with phospholipid vesicles (liposomes), such as high cost, stringent storage condition and the oxidative degradation of phospholipids[18].

Glaucoma is a disease with a characteristic of higher level of intraocular pressure (IOP) which might progressively hurt visibility. The average IOP of population is 15.5 ± 2.57 mmHg. If people whose IOP is 20.5 mmHg or higher could be suspected of having glaucoma and IOP over 24 mmHg is a definite case of glaucoma[19]. The chronic glaucoma with open angle poses a major problem of public health and it is the second leading cause of blindness in the world[20]. It touches approximately 1-2% of the population with age more than 40 years and its incidence increases with the age[21]. Its treatment requires a long and prolonged therapy by eye medication and thus, niosomes could be a useful vesicular system for the treatment of glaucoma. The present review highlights varoius complications of glaucoma therapy with mostly available and/or newer drugs, novel strategies in the development of anti-glaucomatic niosomal systems and the challenges standing ahead.

COMPLICATIONS OF GLAUCOMA THERAPY

The most available anti-glaucoma drugs have been listed in Table 1. Many ongoing clinical studies are trying to find neuroprotective agents (memantine, glatiramer acetate) that might benefit the optic nerve and certain retinal cells in glaucoma. The treatment of open-angle glaucoma and secondary glaucoma is primarily with drugs, whereas the narrow-angle or congenital types is primarily surgical. Long-term use of ocular drugs, as in glaucoma patients who are treated for decades after they are diagnosed, frequently causes tear film and conjunctival involvement, sometimes resulting in sight-threatening ocular surface disorders[22-25]. Moreover, higher concentration of some drugs causes allergy at the ocular surface such as α_2-agonist brimonidine shows concentration dependent allergy due to oxidation of the drug[26]. Prolonged use of eye medications with preservatives presents a certain risk to ocular surface, such as thickness of sub-epithelial collagen of conjunctiva[27], a chronic sub-clinical inflammation as shown by the presence of immunologic changes and inflammatory infiltrates[28]. Medications

placed in the eye are absorbed into the conjunctival blood vessels on the eye surface. A certain percentage of the active ingredient of the medication, though small, will enter the blood stream and may adversely affect functions such as heart rate and breathing. Hence, there is a need to develop an alternative ophthalmic preparation and in this context, niosomal preparations may be the alternative.

FORMULATION ASPECTS OF ANTI-GLAUCOMATIC NIOSOMES

Niosomes are formed by self-assembly of non-ionic surfactants in aqueous media as spherical, unilamellar, multilamellar system and polyhedral structures in addition to inverse structures which appear only in non-aqueous solvent[29].

Surfactants

Van Abbe[30] explained that the non-inonic surfactants are preferred because the irritation power of surfactants decreases in the following order: cationic> anionic> ampholytic> non-ionic. The ether type surfactants with single alkyl chain as hydrophobic tail, is more toxic than corresponding dialkylether chain[31]. The ester type surfactants are chemically less stable than ether type surfactants and the former is less toxic than the latter because ester-linked surfactant is degraded by esterase to triglycerides and fatty acid *in vivo*[31]. The surfactants with alkyl chain length from C_{12}-C_{18} are suitable for the preparation of niosomes[32]. Span series surfactants having hydrophilic lipophilic balance (HLB) number of between 4-8 can form vesicles[33]. Guinedi et al.[34] prepared niosomes from Span 60 and Span 40 to encapsulate acetazolamide (ACZ). Highest drug entrapment efficiency was obtained with Span 60 in a molar ratio of 7: 6 with cholesterol. They found that both the surfactants were non-irritant with ocular tissues however; only reversible irritation of substantia propia was observed in the rabbit eye.

Table 1: The commonly used anti-glaucoma drugs and their mechanism of action

Drug	MOA	FDA approved medication
Prostaglandins (lanatoprost, travoprost)	better outflow of fluids	Lumigan (Allergan), Travatan (Alcon), Rescula (Novartis), Xalatan (Pfizer)
Beta-blockers (timolol, betaxolol, levobunolol)	decreasing fluid production	Timoptic XE (Merck), Istalol (ISTA), Betoptic S (Alcon).
Topical carbonic anhydrase inhibitors (dorzolamide, acetazolamide, brinzolamide)	decreasing rate of aqueous humor production	Trusopt (Merck), Azopt (Alcon)
α2 adrenoceptor agonist (brimonidine, apraclonidine)	increasing uveoscleral outflow and decreasing aqueous production	Iopidine (Alcon), Alphagan P (Allergan)
Epinephrine	decreasing the rate of aqueous humor production and increasing the outflow	Propine (Allergan)

Charge inducer

Charge inducer is used to impart charge on the vesicles to increase its stability by preventing fusion of vesicles and providing higher value of zeta potential. The commonly used positively charge inducers are stearylamine, cetyl pyridinium chloride and negatively charge inducers are lipoamino acid and dicetyl phosphate.

Aggarwal and his coworkers[35] formulated niosomes by reverse phase evaporation method to encapsulate ACZ using Span 60, cholesterol, positively (stearyl amine), and negatively (dicetyl phosphate) charge inducers. Drug entrapment efficiency varied with the charge and the percent entrapment efficiency was found to be 43.75%, 51.23% and 36.26% for neutral, positively charged and negatively charged niosomes, respectively. The positively charged niosomes, although showed good corneal permeability and IOP-lowering capacity, were however seemed to be inappropriate in terms of the corneal cell toxicity.

Bioadhesive polymer

Bioadhesive polymers are the other membrane additives that are used to provide some additional properties to the niosomes. Carbopol 934P-coated niosomal formulation of ACZ, prepared from Span 60, cholesterol, stearylamine or dicetyl phosphate exhibited more tendency for the reduction of intraocular pressure compared to that of a marketed formulation (Dorzox)[35]. Aggarwal and Kaur[36] prepared chitosan and carbopol-coated niosomes to entrap anti-glaucoma agent timolol maleate by reverse phase evaporation method. Polymer coating extended the drug release up to 10 h (releasing only 40-43% drug). However, in comparison, chitosan-coated niosomes showed a better sustained effect.

Steric Barrier

Some researchers[37] examined the aggregation behavior of monomethoxypoly (ethylene glycol) cholesteryl carbonates in mixture with diglycerol hexadecyl ether and cholesterol. They obtained non-aggregated, stable, unilamellar vesicles at low polymer levels with optimal shape and size homogeneity at cholesteryl conjugate/lipids ratios of 5-10 mol%. Higher levels up to 30 mol% led to the complete solubilization of the vesicles into disk-like structures of decreasing size with increasing polyethylene glycol content. This study revealed the bivalent role of the derivatives; while behaving as solubilizing surfactants, they provided an additional efficient steric barrier, preventing the vesicles from aggregation and fusion over a period of at least 2 weeks.

Isotonic stabilizer

Development of a topically effective formulation of ACZ is difficult because of its unfavorable partition coefficient, solubility, permeability coefficient, and poor stability at the pH of its maximum solubility. Based on these factors and the ability of niosomes to come into complete contact with corneal and conjunctival surfaces, niosomal drug delivery system has been investigated to enhance the corneal absorption of ACZ. Boric acid solution (2%) is isotonic with tears and could be used as a vehicle for the ACZ niosomal formulations because the pH of maximum stability for ACZ is 4.0. A recent study revealed that boric acid solution can maintain the pH between 4.0 and 5.0. In addition, the pharmacodynamic studies showed more than 30% fall in IOP which was sustained up to 5 h[38].

Method of preparation

This affects mainly the vesicle lamellarity, entrapment efficiency, and size. For example, reverse phase evaporation method produces large unilameller vesicles appropriate for higher entrapment of water soluble drugs. Film hydration method produces multilamellar niosomes which after sonication gives unilamellar niosomes. Recently, it has been reported that reverse phase evaporation method afforded the maximum drug entrapment efficiency (43.75%) as compared with ether injection (39.62%) and film hydration (31.43%) methods[35]. Vyas et al.[39] prepared discoidal vesicles (discome) by treating niosomes with solulan C24 (poly-24-oxyethylene cholesteryl ether). Discosomes were of larger sizes (12-60 μm) and these entrapped higher quantity of timolol maleate. Their disc sizes provided better ocular localization. The discomes were found to be promising for controlled ocular administration of water soluble drugs.

***IN VITRO-IN VIVO* CORRELATION (IVIVC): NEED AND PROGRESS**

A key goal in pharmaceutical development of dosage forms is a good understanding of the *in vitro* and *in vivo* performance of the dosage forms. One of the challenges of biopharmaceutical research is correlating *in vitro* drug release information of drug formulations to the *in vivo* drug profiles (IVIVC). Thus the need for a tool to reliably correlate *in vitro* and *in vivo* drug release data has exceedingly increased. Such a tool shortens the drug development period, economizes the resources and leads to improved product quality.

Increased activity in developing IVIVC indicates the value of IVIVC to the pharmaceutical industry. IVIVC can be used in the development of new pharmaceuticals to reduce the number of human studies during the formulation development because the main objective of an IVIVC is to serve as a surrogate for *in vivo* bioavailability and to support biowaivers[40]. It is nothing but a mathematical model which relates the *in vitro* drug release with *in vivo* permeation. A good correlation value will indicate better ocular bioavailability. Shoenwald and Huang[41] reported the log permeability coefficients as a sum of log coefficients of β-blocker as functions of partition coefficient, molecular weight and/or degree of ionization. After conducting the permeability study with isolated rabbit corneal or scleral membrane using two-chamber glass diffusion cell, Ahmad et al.[42] suggested that scleral permeability of drugs like timolol, pindolol was greater than that of cornea. However, recent trend of permeation study is based on cell line. Carrier mediated pathway for potent anti-glaucoma agent, brimonidine has been discovered by studying its absorption *via* ARPE-19 cell, human retinal pigmented epithelium (RPE) cell line on transwell filters[43].

CONCLUSION

In the last couple of years, continuous research have been going on for better delivery of anti-glaucoma drugs with the aim of more localized drug delivery, minimization of dosing frequency. An ophthalmic should preferably release drug at a controlled rate to prolong the effect in reducing IOP and should be nontoxic and comfortable for patient use. Niosomal system could afford such characteristics and could be a useful ocular delivery system for anti-glaucoma drugs. World health organisation (WHO) World Health Bulletin 2002 declared that 12.30% of total blindness would be because of glaucoma. However, the situation will be worsening because large number of people will fall into the geriatric group. In these consequences, more research should be continued with niosomes for the effective glaucoma therapy.

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