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CURRENT TREND IN OPHTHALMIC DRUG DELIVERY: ANTIGLAUCOMATIC NIOSOMAL GEL

Neelam Jain*, Neeraj Jain[1], Shubhrat Maheshwari[2], Ravi Kumar[3], Richa Shakya[4], Pratiksha Jayaswal[5]

*Faculty of Pharmacy, Oriental University, Indore-453555, M.P., India.
[1]Teerthankar Mahaveer College of Pharmacy, TMU, Moradabad- 244001, U.P., India.
[2]Rajarshi Rananjay Sinh College of Pharmacy, Amethi-227405, U.P., India.
[3]Narayan Institute of Pharmacy, Gopal Narayan Singh University, Jamuhar, Sasaram-821305, Bihar, India.

[4]Noida Institute of Engineering and Technology, Knowledge Park -2, Greater Noida-201306, U.P., India.

[5]Faculty of Pharmaceutical sciences Rama University, Mandhana, Kanpur-209217, U.P., India.

***Corresponding author name:** Neelam Jain
***Corresponding author address:** Faculty of Pharmacy, Oriental University, Indore-453555, Madhya Pradesh, India.
Email id: neelamnj02@gmail.com
Contact no: +91-8982753610

ABSTRACT

Glaucoma is a prevalent neurodegenerative disorder characterized by increased intraocular pressure (IOP) and subsequent retinal ganglion cell (RGC) death leading to the loss of visual field. The chronic open angle glaucoma creates a major problem of public health and it is second to cataract as a leading cause of global blindness. Its treatment requires a long and prolonged therapy by eye medication. The major drawbacks associated with eye drops are lack of drug permeability through ocular barrier and poor bioavailability. The reason may be attributed to precorneal loss caused by tear turnover, nasolacrimal drainage, reflex blinking, and ocular static and dynamic barriers. With the recent advancement in the field of ocular therapy, drug delivery approaches have been elevated to a new concept in terms of nonionic surfactant vesicles (Niosomes). Nowadays, niosomes are gaining more popularity because of their stability, ease of preparation, achieving reduced toxicity, increasing drug efficacy and most importantly their site targeted action. Moreover, niosomes based ocular gel containing bioadhesive polymer helps the drug to remain adhered to eye surface for a long period of time. Hence, precorneal residence time is increased, resulting in significant enhancement of ocular bioavailability. This article covers

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structure of eye, drawbacks of conventional ocular preparations, complications of glaucoma therapy and newer advances in the field of antiglaucomatic niosomal gel.

KEYWORDS: Niosomes, Glaucoma, Ocular delivery, Eye drops, Niosomal gel.

INTRODUCTION

Eye is the window of our soul. The eye is a complex organ with a unique anatomy and physiology [1]. It has a special attribute that allows local drug delivery and non-invasive clinical assessment of disease but also makes understanding disease pathogenesis and ophthalmic drug delivery challenges [2]. Eye ailments can cause distress and trouble in patients, with the ultimate fear of vision loss or even facial disfigurement [3]. Many parts of the eye are relatively inaccessible to systemically administered drug and, as a result, topical drug delivery remains the most preferred route in most of the cases. Drugs may be delivered to treat the precorneal region for such infections as conjunctivitis and blepharitis or to provide intraocular treatment via the cornea for disease such as glaucoma and uveitis [4].

The most convenient way of delivering drugs to the eye is in the form of eye drops. The major drawbacks associated with eye drops are lack of drug permeability through ocular barrier and poor bioavailability. The reason may be attributed to precorneal loss caused by tear turnover, nasolacrimal drainage, reflex blinking, and ocular static and dynamic barriers. Only about 1-3% of the drug penetrates cornea and reaches the intraocular tissues while major portions are absorbed via conjunctiva and nasal mucosa [5], which may result in some undesirable side effects [6]. Only a small amount is available for its therapeutic effect resulting in frequent dosing[7,8]. In addition, the ocular residence time of conventional eye drops islimited to a few minutes due to lacrimation and blinking[9]; and the ocularabsorption of a topicallyapplied drug is reduced to appr oximately l-10%[10].

In order to overcome the problems of conventional ocular therapy, numerous nanocarriers such as liposomes, micelles etc. have been developed. But due to blurred vision or lack of stability and patient compliance, these systems have not been universally accepted. With the recent advancement in the field of ocular therapy, drug delivery approaches have been elevated to a new concept in terms of nonionic surfactant vesicles (Niosomes). Nowadays niosomes are gaining more popularity because of their stability, ease of preparation, achieving reduced toxicity, increasing drug efficacy and most importantly their site targeted action [11]. Vesicular drug delivery systems used in ophthalmics such as niosomes not only helps in providing prolonged and controlled action at the corneal surface but also preventing the metabolism of the drug by enzymes present at the tear/corneal surface [12]. Drug enclosed in the vesicles allows for an improved partitioning and transport through the cornea.

Recently, controlled and sustained drug delivery has become the standard in modern pharmaceutical design and an intensive research has been under taken in achieving much better drug product effectiveness, reliability and safety. In this regard, many bioadhesive polymers are useful which undergo reversible sol to gel phase transition in response to physiological stimuli

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[13]. *In-situ* gels are conveniently dropped as a solution into the conjunctival sac, where they undergo a transition into a gel with its favourable residence time.

Niosomes, administered as an ophthalmic *in-situ* gel, are capable of localizing and maintaining drug activity at its site of action due to their easy transition through ocular barrier with reduced drug frequency and toxicity [14]. Moreover, niosomes based ocular gel containing bioadhesive polymer helps the drug to remain adhered to eye surface for a long period of time. Hence, precorneal residence time is increased, resulting in significant enhancement of ocular bioavailability [15, 16].

STRUCTURE OF EYE

The structure of eye can be divided into two main parts: anterior segment and posterior segment. Anterior segment of the eye occupies approximately one-third while the remaining portion is occupied by the posterior segment. Tissues such as cornea, conjunctiva, aqueous humor, iris, ciliary body and lens make up the anterior portion. Back of the eye or posterior segment of the eye include sclera, choroid, retinal pigment epithelium, neural retina, optic nerve and vitreous humor. The anterior and posterior segment of eye is affected by various vision threatening diseases. Diseases affecting anterior segment include, but not limited to glaucoma, allergic conjunctivitis, anterior uveitis and cataract. While, age-related macular degeneration (AMD) and diabetic retinopathy is the most prevalent diseases affecting posterior segment of the eye [17]. The structure of eye was shown in Fig. 1 and the detailed description of each eye part is given below:

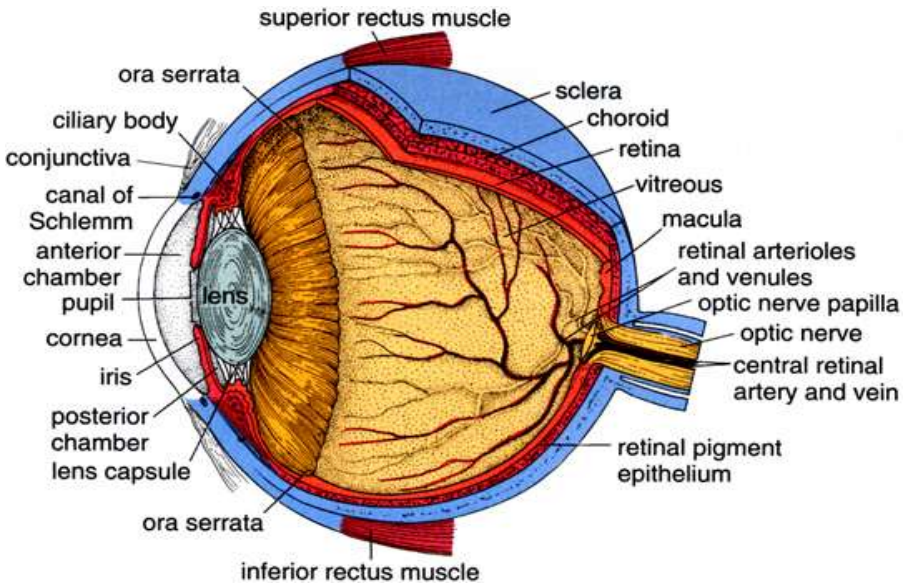

Fig. 1: Anatomy and physiology of eye [18]

Aqueous humour

The aqueous humor is a jelly-like substance located in the outer/front chamber of the eye. It is a watery fluid that fills the "anterior chamber of the eye" which is located immediately behind the cornea and in front of the lens. The aqueous humor is very slightly alkaline salt solution that includes tiny quantities of sodium and chloride ions. It is continuously produced, mainly by the

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ciliary processes, flows from the posterior chamber through the pupil into the anterior chamber, and exits via the trabecular route at the angle and the uveoscleral route. Schlemm's canal (canal of Schlemm or the scleral venous sinus), is a circular channel that collects aqueous humour from the anterior chamber and delivers it into the bloodstream via the anterior ciliary veins. It is located at the junction of the cornea and the sclera. In human, the rate of aqueous humor turnover is approximately 1%-1.5% of the anterior chamber volume per minute. The rate of aqueous formation is approximately 2.5 µl/min. Aqueous humor consists of pressure dependent and pressure independent pathways. The pressure dependent outflow refers to the trabecular meshwork-schlemm's canal-venous system, while pressure independent outflow refers to any non-trabecular outflow and is called as uveoscleral outflow [19].

Conjunctiva

The conjunctiva protects the eye and also involved in the formation and maintenance of the precorneal tear film and in the protection of the eye. The conjunctiva is a thin transparent membrane lies in the inner surface of the eyelids and that is reflected onto the globe. The conjunctiva is made of an epithelium, a highly vascularised substantia propria, and a submucosa. The bulbar epithelium contains 5-7 cell layers. The structure resembles a palisade and not a pavement corneal epithelium cells are connected by tight junctions, which render the conjunctiva relatively impermeable. The human conjunctiva is about 2 and 30 times more absorption of drugs than the cornea and also proposed that loss of drug by this route is a major path for drug clearance. The highest density of conjunctiva is due the presence of 1.5 million globlet cell varying with age depended among the intersujects variability and age. The vernal conjunctivitis and atopic kerato conjunctivitis occurs due to the great variation in goblet cell density results only in a small difference in tear mucin concentration [20].

Cornea

The cornea is a strong clear transparent bulge located at the front of the eye that conveys images to the back of the eyes. The cornea is convex anteriorly and is involved in refracting light rays to focus them on the retina. The front surface of the adult cornea has a radius of approximately 8 mm that covers about one-sixth of the total surface of the eye ball. It is a vascular tissue to which nutrient and oxygen are supplied via bathing with lachrymal fluid and aqueous humour as well as from blood vessels that lines the junction between the cornea and sclera [21].

Pupil

Pupil generally appears to be the dark "centre" of the eye, but can be more accurately described as the circular aperture in the centre of the iris through which light passes into the eye. The size of the pupil (and therefore the amount of light that is admitted into the eye) is regulated by the pupillary reflex (also known as the "light reflex"). As the size of iris increases (or decreases) the size of the pupils decreases (or increase) correspondingly.

Iris

The iris is the visible colored part of the eye (shades may vary individually like blue, green, brown, hazel, or grey) and extends anteriorly from the ciliary body, lying behind the cornea and in front of the lens. The iris is a diaphragm of variable size whose function is to adjust the size of

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the pupil to regulate the amount of light admitted into the eye. It divides the anterior segment of the eye into anterior and posterior chamber which contains aqueous fluid secreted by the ciliary body. The iris is supplied by parasympathetic and sympathetic nerves. Parasympathetic stimulation constricts the pupil and sympathetic stimulation dilates it.

Ciliary muscle

The ciliary muscle is a ring of striated smooth muscles in the eye's middle layer attached to iris. It is important because contraction and relaxation of the ciliary muscle controls the shape of the lens. This process may be described simply as the balance existing at any time between two states: ciliary muscle relaxed (This enables the eye to focus on distant objects) and ciliary muscle contracted (This enables the eye to focus on near objects).

Lens

The lens is a transparent structure enclosed in a thin transparent capsule. It is located behind the pupil of the eye and suspended from the ciliary muscles by the zonule fibers. It helps to refract light travelling through the eye (which first refracted by the cornea). The lens focuses light into an image on the retina. It is able to do this because the shape of the lens is changed according to the distance from the eye of the object(s) the person is looking at. This adjustment of shape of the lens is called accommodation and is achieved by the contraction and relaxation of the ciliary muscles.

Vitreous humor

The vitreous humour (vitreous body) is a perfectly transparent thin jelly like substance that fills the chamber behind the lens of the eye. It is an albuminous fluid enclosed in a delicate transparent membrane called the hyaloid membrane. It is located in the large area that occupies approximately 80% of each eye in the human body.

Retina

The retina is located at the back of the human eye. The retina may be described as the "screen" on which an image is formed by light that has passed into the eye via the cornea, aqueous humour, pupil, lens, then the hyaloids and finally the vitreous humour before reaching the retina. The retina contains photosensitive elements (called rods and cones) that convert the light they detect into nerve impulses that are then sent onto the brain along the optic nerve. The function of the retina is not just to be the screen onto which an image may be formed but also to collect the information contained in that image and transmit it to the brain in a suitable form for use by the body. The retinal "screen" is therefore a light sensitive structure lining the interior of the eye. It contains photosensitive cells (called rods and cones) and their associated nerve fibers that convert the light they detect into nerve impulses that are then sent onto the brain along the optic nerve.

Macula

The center of the retina is called the macula. The macula contains a high concentration of photoreceptor cells which convert light into nerve signals. Because of the high concentration of

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photoreceptors, we are able to see fine details such as newsprint with the macula. At the very center of the macula is the fovea, the site of our sharpest vision.

Sclera

The sclera is tough white sheath around the outside of the eye-ball. It is a firm fibrous membrane that maintains the shape of the eye as an approximately globe shape. It is much thicker towards the back/posterior aspect of the eye than towards the front/anterior of the eye [22].

Choroid

The choroid layer is located behind the retina and absorbs unused radiation and nourishes the outer portions of the retina. It is a thin, highly vascular (i.e. it contains blood vessels) membrane that is dark brown in colour and contains a pigment that absorbs excess light and so prevents blurred vision (due to too much light on the retina). The choroid has one of the highest blood flows in the body. The choroid is loosely attached to the inner surface of the sclera by the lamina fusa.

Optic nerve

The optic nerve is the second cranial nerve and is responsible for vision. Each nerve contains approximately one millions fibers transmitting information from the rod and cone cells of the retina. The front surface of the optic nerve, which is visible on the retina, is called the optic disk.

Papilla

The papilla is also known as the “blind spot” and is located at the position from which the optic nerve leaves the retina.

Retinal pigmented epithelium (RPE)

A layer of cells that protects and nourishes the retina, removes waste products, prevents new blood vessel growth into the retinal layer and absorbs light not absorbed by the photoreceptor cells; these actions prevent the scattering of the light and enhance clarity of vision.

Nasolachrymal drainage system

Nasolachrymal drainage system consists of three parts; the secretory system, the distributive system and the excretory system. The secretory portion is composed of the lacrimal gland that secreted tears are spread over the ocular surface by the eyelids during blinking. The secretory system is stimulated by blinking and temperature change due to the tear evaporation and reflux secretors that have an efferent parasympathetic nerve supply and secrete in response to physical and emotional state e.g. crying. The distributive system consists of the eyelids and the tear meniscus around the lid edges of the open eye, which spread tears over the ocular surface by blinking, thus preventing dry areas from developing. The excretory part of the nasolachrymal drainage system consists of the lachrymal puncta, the superior, inferior and common canaliculi; the lachrymal sac, and then nasolachrymal duct. In humans, the two puncta are the openings of the lachrymal canaliculi and are situated on an elevated area known as the lachrymal papilla. It is thought that tears are largely absorbed by the mucous membrane that lines the ducts and the lachrymal sac; only a small amount reaches the nasal passage [23].

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Tear film

A thin fluid layer is covered the exposed part of the eye called as precorneal tear film. The film thickness is about 3-10 µm depending on the measurement method with the resident volume approximately 10 µl. The osmolality of the tear fluid is approx. 310-350 mOsm/kg in normal eyes and is maintained by the monovalent and divalent inorganic ions present in fluid such as Na+, K+, Cl−, HCO_3^-, and proteins. The mean pH of normal tears is about 7.4. Diurnal patterns of pH changes the pH of tear, which a general shift from acid to alkaline during the day. The buffer capacity of the tears fluid is determined by bicarbonate ions, proteins, and mucins [24, 25]. Tears exhibit a non- Newtonian rheological behaviour. The viscosity is about 3 mPa.s [26].

GLAUCOMA

Glaucoma is a prevalent neurodegenerative disorder of the eye. Increased intraocular pressure (IOP) and subsequent retinal ganglion cell (RGC) death leading to the loss of visual field characterizes the pathology of primary open angle glaucoma (POAG), which is the most common form. The disease affects over 66 million people worldwide, causing bilateral blindness in 6.8 million [27]. Patients with POAG typically exhibit increased resistance to the outflow of aqueous humor through the trabecular meshwork, which can result in an increase in IOP and subsequent cell death from compression of the optic nerve axons [28]. However, IOP is the primary risk factor causing the loss of RGCs; the strategies of treatment mostly involve lowering IOP [29]. Glaucoma is second to cataract as a leading cause of global blindness. It touches approximately 1-2% of the population with age more than 40 years and its incidence increases with the age [30]. Glaucoma is caused by a number of different eye diseases that in most cases produce increased pressure within the eye. This elevated pressure is caused by a backup of fluid in the eye as shown in Fig. 2.

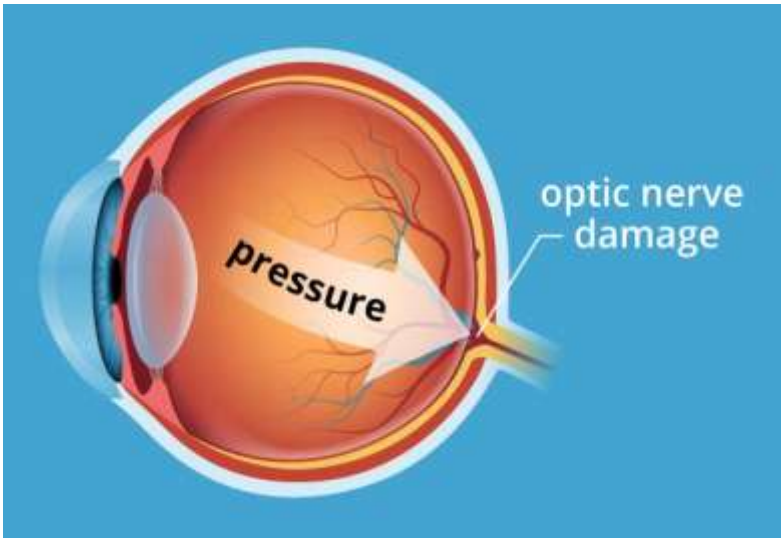

Fig. 2: Development of glaucoma [31]

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TYPES OF GLAUCOMA [32]

There are a variety of different types of glaucoma. The most common forms are:

Open-angle glaucoma

Open-angle glaucoma has no symptoms at first. It is a progressive disease characterized by optic nerve damage. High eye pressure is the most significant recognized risk factor for the development and progression of the disease. The pressure in the eye builds up gradually leading damage to the optic nerve, loss of side (peripheral) vision, and without treatment, total blindness.

Closed-angle glaucoma

Closed-angle glaucoma comes in two forms, acute or chronic. Acute closed-angle glaucoma is a medical emergency that must be treated immediately or blindness can result in one or two days. In acute closed angle glaucoma the normal flow of aqueous humor between the iris and the lens suddenly becomes blocked. Symptoms may include severe pain, nausea, vomiting, and blurred vision. The patient may also see coloured halos around lights. Chronic closed-angle glaucoma progresses slowly and can produce damage without symptoms, similar to open-angle glaucoma.

Congenital glaucoma

Congenital glaucoma occurs in infants, who are born with defects that prevent the normal drainage of the aqueous humor.

Normal tension glaucoma

Normal-tension glaucoma, also known as low-tension glaucoma, is characterized by progressive optic nerve damage and visual field loss with a statistically normal intraocular pressure. This form of glaucoma, which is being increasingly recognized, may account for as many as one-third of the cases of open-angle glaucoma in the United States. Normal-tension glaucoma is thought to be related, at least in part, to poor blood flow to the optic nerve, which leads to death of the cells that carry impulses from the retina to the brain. In addition, these eyes appear to be susceptible to pressure-related damage even in the high normal range, and therefore a pressure lower than normal is often necessary to prevent further visual loss.

Secondary glaucoma

Secondary glaucoma can be open or closed-angle, and results from some other eye disorder or medical problem, such as inflammation, a tumour, or trauma.

PROBLEMS IN GLAUCOMA THERAPY

Various drugs are available for the treatment of glaucoma. The mostly used anti-glaucoma drugs have been listed in Table 1. The treatment of open angle glaucoma and secondary glaucoma is primarily with drugs, whereas the narrow angle or congenital types is primarily surgical. Current treatment options primarily aim at decreasing IOP by utilizing pharmacological agents, laser therapy and surgery. The method of reducing IOP is by enhancing the outflow of humor from the eyes through the use of muscarinic acetylcholine receptor agonists [33]. Pilocarpine hydrochloride is a drug used in the treatment of chronic open-angle glaucoma and acute angle-closure glaucoma for over 100 years [34]. It is a parasympathomimetic alkaloid obtained from the leaves of tropical South American shrubs from the genus *Pilocarpus*. It is a non-selective muscarinic

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receptor agonist in the parasympathetic nervous system, which acts therapeutically at the muscarinic acetylcholine receptor M_3, found on the iris sphincter muscle, causing the muscle to contract resulting in pupil constriction (miosis). Pilocarpine hydrochloride also acts on the ciliary muscle and causes it to contract. When the ciliary muscle contracts, it opens the trabecular meshwork through increased tension on the scleral spur. This action facilitates the rate that aqueous humor leaves the eye to decrease intraocular pressure [35]. The major drawbacks associated with pilocarpine HCl, administered as an eye drop, was its low ocular bioavailability (1-3%) and short precorneal residence time. Moreover, higher concentration of some drugs causes allergy at the ocular surface such as α2-agonist brimonidine shows concentration dependent allergy due to oxidation of the drug. 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 bloodstream and may adversely affect functions such as heart rate and breathing. Unfortunately, the major part of the drug does not penetrate into the eye but it is lost by physiological drainage (non-productive loss). Its treatment requires a long and prolonged therapy by eye medication. Thus, these problems can be minimized by the use of niosomal vesicular system for the successful treatment of glaucoma.

Table 1: Commonly used anti-glaucoma drugs

Drug	**FDA approved medication**
Miotics (Pilocarpine, Carbachol)	Isopto®Carpine, Pilocar®, Pilopine HS®
Prostaglandins (Lanatoprost, Travoprost)	Xalatan®, Travatan®
Beta-blockers (Timolol, Betaxolol, Levobunolol)	Timoptic®,Istalol®, Betoptic®, Betagan®
Carbonic anhydrase inhibitors (Acetazolamide, Dorzolamide)	Diamox®, Trusopt®, Neptazane®
α2 adrenoceptor agonist (Brimonidine, Apraclonidine)	Alphagan®, Iopidine®
Epinephrine	Epifrin®, Eppy-N®, Dipivefrin Propine®

NIOSOMES

Niosomes are formed from the self-assembly of non-ionic amphiphiles in aqueous media resulting in closed bilayer structures [36], which can entrap both hydrophilic and lipophilic drugs either in an aqueous layer or in vesicular membrane [37]. Basically niosomes are formulated by using cholesterol and non-ionic surfactant. The surfactant molecules tend to orient themselves in such a way that the hydrophilic ends of the non-ionic surfactant point outwards, while the hydrophobic ends face each other to form the bilayer [38] as shown in Fig. 3. Major component of niosomes is non-ionic surfactant which give it an advantage of being more stable when compared

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to liposomes thus overcoming the problems associated with liposomes i.e. susceptibility to oxidation, high price and the difficulty in procuring high purity levels which influence size, shape and stability [39].

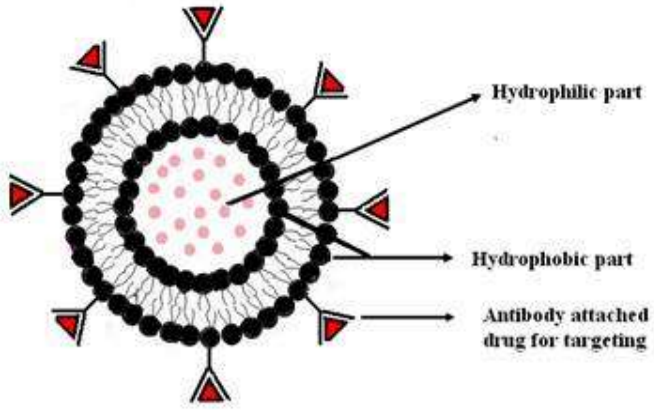

Fig. 3: Structure of niosome [40]

NIOSOMES IN OCULAR DRUG DELIVERY

The eye is protected by three highly efficient mechanisms (a) an epithelial layer that is a formidable barrier to penetration (b) tear flow (c) the blinking reflex. All the three mechanisms are responsible to inhibit proper drug penetration into the deeper layers of the cornea and the aqueous humour [41]. There is also rapid wash out of drugs from the corneal surface due to lacrimal secretion. Various drug delivery strategies have been considered for numerous advantages over conventional ocular drug therapy but not overcoming of drawbacks like poor patient compliance and difficulty of insertion as in ocular inserts, tissue irritation, and damage caused by penetration enhancers, collagen shields and change in pharmacokinetic and pharmacodynamics of the drug, which is caused by altering the chemical structure of the drug (prodrug approach). Niosomes can affect physical properties of drug products such as viscosity, film spreading, and film strength and improve the action [42].

Niosomes have been widely used in the ocular drug delivery for the treatment of various disorders and infections such as inflammation, dry eye, allergy, ocular hypertension and glaucoma. Niosomes in topical ocular delivery are preferred over other vesicular systems because of their: (1) chemical stability; (2) low toxicity because of their nonionic nature; (3) handling surfactants with no special precautions or conditions; (4) the ability to improve the performance of the drug via better availability and controlled delivery at a particular site; (5) being biodegradable, biocompatible, and non-immunogenic [43]. Drug loaded niosomes constitute a versatile drug delivery system, with the ability to overcome physiological barriers and guide the drug to specific cells or intracellular compartments either by passive or ligand-mediated targeting mechanisms.

Niosomes could be a potential carrier for the effective treatment of glaucoma in a controlled manner. Niosomes in combination with mucoadhesive polymers (niosomal *in-situ* gel) show a controlled as well as a prolonged effect. Prolonging the drug contact time with the surface of the

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eye can also increase their penetration through the cornea, hence increasing the accessibility of the drug to aqueous humor thereby enhancing ocular bioavailability.

NIOSOMAL GELS

Niosomal *in-situ* gels proved to be one of the successful approaches to accomplish the goals successfully. The development of niosomal gel systems has received considerable attention over the past few years. This novel drug delivery system promotes the importantly ease and convenience of administration, deliverance of accurate dose as well as to prolong residence time of drug in contact with eye surface, that problems generally encountered in ocular dosage forms. Gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange [44]. Smart polymeric systems represent promising means of delivering the drugs; these polymers undergo sol-gel transition, once administered. Various natural and synthetic polymers are used for formulation development of *these* systems [45].

The *in-situ* gelling systems for ophthalmic use can be classified as pH sensitive, temperature sensitive and ion-activated systems. Carbopol is a well-known pH dependent polymer, which stays in solution form at acidic pH but forms a low viscosity gel at alkaline pH. HPMC is used in combination with carbopol to impart the viscosity to carbopol solution, while reducing the acidity of the solution.

Temperature-sensitive hydrogels are probably the most commonly studied class of environment sensitive polymer systems in drug delivery research. The use of biomaterial whose transitions from sol-gel is triggered by increase in temperature is an attractive way to approach *in-situ* formation. Pluronics are poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide) (PEO-PPOPEO) triblock co-polymer that are fluid at low temperature, but forms thermo responsible gel when heated as a consequences of a disorder-order transition in micelle packing which makes these polymers suitable for *in-situ* gelation [46].

The ion-activated gelling system can be formulated using locust bean gum, a natural hydrophilic bio-polymer, which is hygroscopic as well as hydrocolloid in nature. It is comprised of a high molecular weight polysaccharides composed of galactomannans consisting of a linear chain of (1→4)-linked β-D-mannopyranosyl units with (1→6)-linked α-D-galactopyranosyl residues as side chains [47], which forms a gel in the cul-de-sac lead to increase the viscosity of a drug formulation in the precorneal region results in increased bioavailability, due to slower drainage from the cornea. Thus, with the use of *in-situ* gelling systems, residence time of the drug in the eye is increased.

FORMULATION ASPECTS OF ANTIGLAUCOMATIC NIOSOMAL GEL

Surfactants

Van Abbe [48] explained that the non-ionic 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 dialkyl ether chain [49]. 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.* The surfactants with alkyl chain

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length from C12-C18 are suitable for the preparation of niosomes [50]. Span series surfactants having HLB number in between 4-8 can form vesicles [51]. Guinedi et al [52] 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.

Charge inducer

Charge inducer is used to impart charge on the vesicles to increase its stability by preventing fusi on 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 co-workers [53] 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 charge niosomes, respectively. The positively charged niosomes, although showed good corneal permeability and IOP lowering capacity. However, it 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) [53]. Aggarwal and Kaur [54] prepared chitosan and carbopol-coated niosomes to entrap antiglaucoma agent timolol maleate by reverse-phase evaporation method. Polymer coating extended the drug release up to 10h (releasing only 40-43% drug). However, chitosan-coated niosomes showed a better sustained effect.

Isotonic stabilizer

Development of a topically effective formulation of ACZ is difficult because of its unfavourable 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 in 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 and 5. In addititon, the pharmacodynamics studies showed more than 30% fall in IOP which was sustained up to 5h [55].

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 ofwater soluble drugs. Film hydration method produces multilamellar niosomes which after Sonication gives unilamellar niosomes. Recently, it has been reported that reverse phase

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evaporation method afforded the maximum drug entrapment efficiency (43.75%) as compared with ether injection (39.62%) and film hydration (31.43%) methods. Vyas *et al* [56] 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 d rugs.

RECENT STUDIES ON NIOSOMAL GELS

Ramadan *et al* [57] developed and investigated timolol maleate loaded niosomal gels for the treatment of glaucoma. The intra-ocular pressure lowering activity of prepared formulations were detected and compared with marketed Timogel. It was concluded from the study that the niosomal gel formulations gave sustained and controlled release of drug and showed higher stability than the niosomes itself. Gel formulation containing 3% CMC Na showed relative bioavailability 1.6 times more than bioavailability of marketed Timogel.

Sathyavathi *et al* [58] formulated and evaluated niosomal in-situ gel of brimonidine tartrate for glaucoma treatment. Antiglaucoma activity of the prepared gel formulations showed more significant and sustained effect in reducing intra ocular pressure than marketed and niosomal drops. Hence niosomal insitu gelling may have its potential applications than the conventional ocular therapy and to improve the ocular bioavailability with minimal loss of drug.

Chaudhari *et al* [59] developed niosomal in-*situ* gel of prednisolone sodium phosphate (PSP) for ocular delivery. The optimized *in-situ* gel containing poloxamer 407 (P407) and poloxamer 188 (P188) in the ratio of 1:2.7 showed gelation temperature at 37^0C (physiological temperature of the body) and t90 value of 10 h thus depicting sustained action. The increased area under curve (AUC) value by 1.75 folds proved increased bioavailability of the drug.

CONCLUSION

Exploitation of polymeric niosomal *in-situ* gels of various drugs for glaucoma treatment provides a number of advantages over conventional ocular dosage forms. Prolonged residence time, good stability, improves bioavailability and biocompatibility characteristics make the *in-situ* gel very reliable. The niosomal gel formulations demonstrated better properties as compared to niosomes itself, indicating a viable alternative to conventional eye drops. 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 drug delivery system should preferably release drug at a controlled rate to prolong the effect in reducing IOP and should be non-toxic and comfortable for patient use. Niosomes containing gels may be considered as promising ocular carriers for the controlled delivery of anti-glaucoma drugs.

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