Ocular Drug Delivery- Recent approaches in the formulation

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ABSTRACT

Ophthalmic products are formulated using essentially the same scientific principles and technology as dosage forms developed for other target organs. Despite numerous scientific efforts, efficient ocular drug delivery remains a challenge for pharmaceutical scientists. Most ocular diseases are treated by topical drug application in the form of solutions, suspensions and ointment. These conventional dosage forms suffer from the problems of poor ocular bioavailability. The major diseases affecting the eye are age-related macular degeneration, diabetic macular edema, cataract, proliferative vitreoretinopathy, uveitis, cytomegalovirus, and glaucoma. A myriad of advances have been made to overcome these physiological barriers for the targeted ocular delivery of drugs. Various approaches that have been attempted to increase the bioavailability and the duration of therapeutic action of ocular drugs can be divided into two categories. The first is based on use of the drug delivery systems, which provide the controlled and continuous delivery of ophthalmic drugs. The second involves, maximizing corneal drug absorption and minimizing precorneal drug loss. This review provides an insight into various noval techniques employed in prolonging the ocular residence time and therefore bioavailability of drugs like mucoadhesive systems, Insitu gelling systems, microemulsions, lipid based nanocarriers, Nanosuspensions, Ocular iontopherosis.

Keywords: Ocular drug delivery, lipid based nanocarriers, Nanosuspensions, Noval techniques, Ocular Bioavailability

INTRODUCTION

Ophthalmic preparations are defined in the United States Pharmacopoeia as sterile dosage forms essentially free from foreign particles, suitably compounded and packaged for instillation into the eye. They include solution, suspension, ointments, and certain solid dosage forms. Solutions and suspensions contain aqueous vehicles. Ointments usually contain a white petrolatum mineral oil base[1]. Ophthalmic products are formulated using essentially the same scientific principles and technology as dosage forms developed for other target organs. Development strategy requires the same considerations for safety, efficacy, stability, and pharmaceutical elegance. As is the case with other pharmaceutical products, ophthalmic products must also comply with applicable regularity regulatory requirements in countries where the products will be marketed.

However, more than 90% of the marketed ophthalmic formulations are in the form of eye drops. These formulations mainly target the anterior segment eye diseases[2]. Most of the topically applied drugs are washed off from the eye by various mechanisms (lacrimation, tear dilution and tear turnover) resulting in low ocular bioavailability of drugs [2]. Moreover, human cornea comprising of epithelium, substantia propria and endothelium also restricts the ocular entry of drug molecules, as a result of these factors less than 5% of administered drug enters the eye [3]

Pre- corneal deficit factors have a crucial role in determining the bioavailability of a drug. These factors can include tear dynamics, impermeability of the corneal epithelium membranes, momentary residence in the fornix conjunctiva and non-specific absorption, among other things [4]. Therefore, a myriad of advances have been made to overcome these physiological barriers for the targeted ocular delivery of drugs. This review provides an insight into various Novel techniques employed in prolonging the ocular residence time and therefore bioavailability of drugs

Ocular Drug Transport

Passive transport or simple diffusion of molecules is a transport process dependent on water and lipid solubility, size of the molecule, and concentration gradient across the cellular membrane. No energy is expended in the process, and transport will cease when the concentrations of the molecules on both sides of the membrane are equal. Passive transport is not inhibited by metabolic inhibitors (inhibiting ATP production or utilization) or by competitive substrates. In general, hydrophilic molecules pass through proteinaceous pores in the cellular membrane and lipophilic molecules diffuse through the lipid portion of the membrane. Transport through the pores is limited by the limited by the pore size that is specific to each tissue. The low lipid

solubility of ionized molecules may be increased by altering the degree of ionization with changes in solution pH. Passive transport is important in diffusion of drugs across the cornea and in nutrient uptake across the corneal endothelium [5].

Active transport is an energy-dependent process requiring ATP, is carrier –mediated, and is capable of transporting substrates against a concentration gradient. Macromolecular carriers are membrane –bound and have varying degrees of substrate specificity. The carrier reversibly binds to the substrate, transports and releases the molecule on the other side of the membrane and returns to the original state. These characteristic also make active transport subject to metabolic inhibitors, Competitive inhibition from other similar substrates, and saturation at high substrate concentrations [6]. Active transport in the corneal endothelium is essential to maintenance of proper stromal hydration. conjunctival and corneal surfaces are lubricated by a film of fluid , pre-corneal tear film , secreted by lacrimal glands . the secretion of the lacrimal gland, the tears , is delivered through number of fine ducts into the conjunctival fornix. The secretion is a clear, watery fluid containing 0.7% protein and the enzyme lysozyme the mucin-protein layer of the film is especially important in maintaining the stability of film. The sebaceous glands of the eyelids secrets an oily fluid that helps to reduce evaporation from the exposed surfaces of the eye by spreading over the tear film, spontaneous blinking replenishes the fluid film by pushing a thin layer of fluid ahead of the lid margins as they come together[7]. *Fornix conjunctiva*, forms the junction between the bulbar and palpebral conjunctivas. It is loose and flexible, allowing the free movement of the lids and eyeball.

Common Diseases Affecting Eye

The structure of eye can be covered under two subheadings (a) anterior segment and (b) posterior segment. Anterior segment consists of front one-third of eye that mainly includes pupil, cornea, iris, ciliary body, aqueous humor, and lens while the posterior segment consists of the back two-thirds of the eye that includes vitreous humor, retina, choroid, macula, and optic nerve. The major diseases affecting the eye are age-related macular degeneration, diabetic macular edema, cataract, proliferative vitreoretinopathy, uveitis, cytomegalovirus, and glaucoma [8-9].

Major Barriers to Topical Ocular Drug Delivery

The exposed part of the eye is covered by a thin fluid layer, the so-called precorneal tear film. The film thickness is reported to be about 3–10 micron depending on the measurement method used. The resident volume amounts to about 10 microlitre [10-13].

According to the three layers theory [13], the precorneal tear film consists of a superficial lipid layer, a central aqueous layer and an inner mucus layer. There are several possible causes of the

barrier behavior of tear film

i) High turnover rate. The basal tear flow is 0.5– 2.2 ml/min. This results in a tear turnover rate of 16% per minute during waking hours. Reflex stimulation might increase lachrymation 100-fold, up to 300 ml/min [14]. Topical administration, mostly in the form of eye drops, is quickly washed away by the tear film after application.

ii) Gel-like mucus layer. Approximately 2–3 ml mucus is secreted daily [15]. Mucin present in the tear film has a protective role by forming a hydrophilic gel layer that moves over the glycocalyx of the ocular surface and clears cell debris, foreign bodies and pathogens [16]. At the same time, it acts as a barrier to drug delivery systems. The epithelium of the cornea consists of 5–6 layers of cells packed closely and connected by tight junctions. These layers form an effective barrier not only to most microorganisms but also to therapeutic drugs. The cornea is composed of five layers, epithelium, Bowman's membrane, stroma, Descemet's membrane, endothelium each of alternating polarity. This sandwich-like structure makes the cornea a crucial barrier to most lipophilic and hydrophilic drugs. To penetrate these layers, optimal lipophilicity for the drug corresponds to logD values (distribution coefficients) of 2–3 [17]. Although intercellular spaces in the conjunctival epithelium are wider than in the corneal epithelium, the cornea and the conjunctiva are rate-limiting factors for water-soluble drugs [18]. Conjunctival blood capillaries and lymphatics can cause significant drug loss into the systemic circulation, thereby lowering ocular bioavailability.

Formulation approaches to improve ocular bioavailability

Various approaches that have been attempted to increase the bioavailability and the duration of therapeutic action of ocular drugs can be divided into two categories. The first is based on use of the drug delivery systems, which provide the controlled and continuous delivery of ophthalmic drugs. The second involves, maximizing corneal drug absorption and minimizing precorneal drug loss. The typical pulse entry type drug release behavior observed with ocular aqueous solutions (eye drops), suspensions, and ointments can be replaced by a more controlled, sustained, and continuous drug delivery, using a controlled release ocular drug delivery system

These systems can achieve therapeutic action with a smaller dose and a fewer systemic and ocular side effects. Such systems include implantable systems [19], ocuserts [20], collagen shields [21] etc., but the limitations of these systems include poor patient compliance, need of surgery, and difficulty in self-insertion. Other approaches include increased viscosity of vehicle, which is based on the fact that by increasing the contact time between the drug and the ocular surface, the bioavailability of the applied drug can be enhanced. Studies to date indicate that this approach

has only limited value, as the formulations are liquid and, therefore, subject to elimination from the eye by all the factors discussed earlier [22]. Novel drug delivery systems, like Insitu gelling systems, Liposomes, nanoparticles and microspheres etc, can also be used to improve the residence time of the drug [23].

Novel drug delivery systems

An ideal ophthalmic formulation should be one that: (1) can be delivered in a drop form without causing blurred vision or irritation; (2) has a suitable strength to endure the lacrimal fluid dilution without rapid precorneal elimination after administration; (3) has a suitable mucoadhesive force to improve the retention of the drug in the precorneal area, thereby facilitating the reservoir effect of the cornea for the drug and increasing the bioavailability.

A major challenge in ocular therapeutics is the improvement of ocular drug bioavailability. Conventional aqueous solutions topically applied to the eye have the inherent disadvantage that most of the instilled drug is lost within the first 15–30s after instillation, due to reflex tearing and drainage via the nasolacrimal duct. Hence, many of the efforts at improving ocular drug delivery have been focused on increasing the duration of the drug contact time. The first step in this direction has been to enhance the precorneal retention of ophthalmic solutions by the incorporation of viscosity building agents such as polyvinyl alcohol and methyl cellulose [24]. However, viscosity has been found to have a minor consequence in prolonging the ocular residence time of drugs. The following are some of the novel techniques employed in prolonging the ocular residence time of drugs.

Mucoadhesive polymers

To improve the ocular bioavailability of drugs, numerous natural and synthetic viscosifying agents were added to the vehicle in order to increase the viscosity of the preparation, to reduce the drainage rate and subsequently to improve the therapeutic efficacy [25-26]. Besides the viscosity increase of the vehicle, Hui and Robinson [27] demonstrated the utility of bioadhesion of polymers for reducing the drainage loss after instillation of ophthalmic formulations, hence improving drug absorption or local action. Polymer-related factors influencing mucoadhesion are hydration or degree of swelling, molecular weight, functional groups, molecular conformation or chain flexibility and mobility, and concentration. The threshold required for successful mucoadhesion is a molecular weight of at least 100,000 Da. Many high molecular weight polymers with different functional groups (such as carboxyl, hydroxyl, amino, and sulfate) capable of forming hydrogen bonds, and not crossing biological membranes, have been screened as a possible excipients in ocular delivery systems.

No significant bioavailability enhancement was reported in humans, as was obtained in rabbits, due to differences in blinking frequency and tolerance [28]. Moreover, rapid drug efflux out of the polymer network occurs [29]. Charged polymers both anionic and cationic demonstrate a better mucoadhesive capacity in comparison to non-ionic cellulose-ethers or polyvinyl alcohol [30-33]. Mucoadhesive Polymer are broadly classified in to three categories

Anionic : Poly(acrylic acid), Carbomer (neutralized), Hyaluronan, sodium carboxy methyl cellulose, Poly(galacturonic acid), sodium alginate, Pectin, Xanthan gum Xyloglucan gum

Cationic: Chitosan

Non-ionic: Scleroglucan, Poloxamer, Hydroxypropylmethylcellulose, Methylcellulose, Poly(vinyl alcohol), Poly(vinyl pyrrolidone)

IN SITU GELLING SYSTEMS

Viscous semi-solid preparations, such as gels and ointments, provide a sustained contact with the eye, but they cause a sticky sensation, blurred vision and induce reflex blinking due to discomfort or even irritation [34-35]. An alternative approach has been the application of in situ gelling systems or phase transition systems, which are instilled in a liquid form and shift to a gel or solid phase in the cul-de-sac. The phase transition is triggered by the pH of the tears, the temperature at the eye surface or the electrolytes present in the tear film [36–39].

pH triggered system

Cellulose acetate hydrogen phthalate latex, typically shows very low viscosity up to pH 5, and form clear gel in few seconds when in contact with tear fluid pH 7.2 to 7.4 and hence, release contents over prolong period of time. Use of such pH sensitive latex described by Gurny et al. the half-life of residence of CAP dispersion on corneal surface was approximately 400 seconds as compare to 40 second for solution. However this system is associated to discomfort patient due to high polymer concentration and low pH of instilled solution [40].

Change in Temperature

Poloxamer F127 is in the form of solution in room temp and when this solution is instilled in to eye phase transition to gel at temp of eye thereby prolonging its consisting of (polyoxyehylene and polyoxypoylene units). No of these units and their ration per mol of polymer provide wide range of polyol with different physical and chemical properties.

Pluronic F127-*g*-poly (acrylic acid) copolymers were studied as *in situ* gelling vehicle for ophthalmic drug delivery system [41]. The rheological properties and *in vitro* drug release of Pluronic-*g*-PAA copolymer gels were investigated. The rheogram and *in vitro* drug release studies indicated that the drug release rates decreased as acrylic acid/Pluronic molar ratio and

copolymer solution concentration increased. But the drug concentration had no obvious effect on drug release. The release rates of the drug from such copolymer gels were mainly dependent on the gel dissolution. *In vivo* resident experiments showed the drug resident time and the total resident amount in rabbit's conjunctiveal sac increased by 5.0 and 2.6 folds for *in situ* gel, compared with eye drops. The decreased loss angle at body temperature and prolonged precorneal resident time also indicated that the copolymer gels had bioadhesive properties.

Hongyi Qi et al [42] investigated a thermosensitive in situ gelling and mucoadhesive ophthalmic drug delivery system containing puerarin based on poloxamer analogs (21% (w/v) poloxamer 407/5% (w/v) poloxamer 188) and carbopol (0.1% (w/v) or 0.2% (w/v) carbopol 1342P NF). The combined solutions would convert to firm gels under physiological condition and attach to the ocular mucosal surface for a relative long time. The incorporation of carbopol 1342P NF not only did not affect the pseudoplastic behavior with hysteresis of the poloxamer analogs solution and leaded to a higher shear stress at each shear rate, but also enhanced the mucoadhesive force significantly. In vitro release studies demonstrated diffusion-controlled release of puerarin from the combined solutions over a period of 8 h. In vivo evaluation (the elimination of puerarin in tear and intraocular pressure-lowering effect) indicated the combined solutions had better ability to retain drug than poloxamer analogs or carbopol alone.

HongBo Yin at el [39] successfully synthesized a biodegradable triblock copolymer poly(ethylene glycol)-poly(*e*-caprolactone)-poly-(ethylene glycol) (PEG-PCL-PEG, PECE), which was flowing sol at low temperature and turned to non-flowing gel at body temperature. The toxicity evaluation of PECE hydrogel as a potential in situ sustained opthalmic drug delivery system was performed, including the biodegradability of PECE hydrogel in the eye, its effect on cultured human lens epithelia, intraocular pressure, and ocular tissues. The results indicated that the prepared PECE hydrogel was biocompatible and biodegradable and safe candidate for sustained ophthalmic drug delivery.

Ion activation

Gelrite® solution, a novel ophthalmic vehicle, gels in the presence of mono or divalent cations. In the conjunctival sac 'ion-activation' of the sol/gel transition is accomplished by the lacrimal fluid. A 0.6% Gelrite® vehicle has been compared to an equi-viscous solution of hydroxyethylcellulose (HEC) using timolol maleate as a drug probe [43]. In vitro release rates of timolol from HEC and Gelrite® gel were similar. In vivo, the formation of the gel prolonged precorneal residence time and increased ocular bioavailability of timolol in the cornea, aqueous humor and iris and ciliary body of albino rabbits.

Zhidong Liu et al prepared an ophthalmic delivery system of an antibacterial agent, gatifloxacin, based on the concept of ion-activated in situ gelation [44]. Alginate (Kelton®) was used as the gelling agent in combination with HPMC (Methocel E50Lv) which acted as a viscosity-enhancing agent. The rheological behaviors of all formulations were not affected by the incorporation of gatifloxacin. Both in vitro release studies and in vivo pre-corneal retention studies indicated that the alginate/HPMC solution retained the drug better than the alginate or HPMC E50Lv solutions alone. These results demonstrate that the alginate/HPMC mixture can be used as an in situ gelling vehicle to enhance ocular bioavailability and patient compliance.

Nono-Gels

Saadia A T et al [92] prepared controlled-release in situ ocular drug-loaded nanoemulsion (NE) gels of Terbinafine hydrochloride using oils (isopropyl myristate/Miglyol® 812), surfactants (Tween® 80/Cremophor® EL), a co-surfactant (polyethylene glycol 400) and water. Drug pharmacokinetics of sterilized Formulation of Miglyol® 812, Cremophor® EL: polyethylene glycol 400 (1:2) and water (5, 55 and 40%, w/w, respectively) In-situ NE gel and oily drug solution were evaluated in rabbit aqueous humor. The gels were transparent, pseudoplastic, Mucoadhesive and showed more retarded zero-order drug release rates with least ocular irritation potential, prolonged mean residence time and increased bioavailability. Maria D. Moya-Ortegaa et al [93] designed and tested In-vivo the sustained release aqueous eye drops of dexamethasone, based on cyclodextrin (CD) nanogels. The nanogel eye drops (containing 25 mg dexamethasone per ml) were tested in rabbits and compared to the commercially available product Maxidex® (suspension with 1 mg dexamethasone per ml). One drop administration of the nanogel eye drops resulted in nearly constant dexamethasone concentration for at least 6 h in the tear fluid whereas the concentration after administration of Maxidex® fell rapidly within 1 to 3hr. The dexamethasone nanogel eye drops were well tolerated with no macroscopic signs of irritation, redness or other toxic effects.

Microemulsions

The main advantage of the microemulsions is the increase in the solubilization of drugs. Siebenbrodt et al[45] determined the maximal percentage for three drugs (indomethacin, chloramphenicol, sodium diclofenac) when dissolved in each of the microemulsion constituents. In an aqueous solution, each constituent of the microemulsion increased the solubility of the three drugs, except for the triacetin of the sodium diclofenac, which is a salt. In addition, the microemulsion strongly improved the solubilization. The choice of the components of the internal phase is an important preliminary step in the establishment of the formulation. In order

to improve the solubilization of the piroxicam and indomethacin, Klang et al and Muchtar et al studied their solubility in several internal phases However, the mixture which allows the optimal solubility of the drugs was not selected for the final formulation for stability reasons, as in the case when oleic acid was used[46-47].

Microemulsions are particularly attractive for delivering hydrophobic drugs to the cornea because of the possibility of loading the drugs in the oil particle [48]. Prednisolone solutions were prepared in self-microemulsifying drug delivery systems. The physical properties of the formulations were observed and the chemical potency of the drug was determined using a stability indicating HPLC method. It was found that water-in-oil microemulsions can protect prednisolone from degradation by gamma ionizing radiation [49]. Microemulsions using Brij 97 were developed for extended delivery of Cyclosporine A (CyA), an immunosuppressant drug that is used for treating a variety of ocular diseases and disorders. Results show that the surfactant and microemulsion-laden gels can deliver CyA at therapeutic dosages for a period of about 20 days [50].

Lipid-Based Nanocarriers

Approximately 90% of the tear film is in the aqueous layer, the function of which is to maintain a smooth ocular surface and provide oxygen for the corneal epithelial cells. The function of the mucous layer is to change the corneal epithelium from hydrophobic to hydrophilic. In this way, the aqueous layer is distributed uniformly across the ocular surface. Lipid-based nanocarriers have properties similar to those of three-layered tear film. After instillation, the continuous phase (water phase) of the emulsion can enhance the aqueous layer of tear film and moisten the cornea. As the oil droplets break down they release encapsulated emulsion components. The oil phase then merges with the natural lipid layer and enhances, reducing evaporative fluid loss. The highly purified oil used in the emulsion causes few side effects and has excellent ocular biocompatibility.

Shen et al [51] prepared an ophthalmic emulsion of flurbiprofen axetil (FBA), a known NSAID, and found that, with the increment of oil content, the mean retention time (MRT) of flurbiprofen(FBA) in aqueous humor was prolonged. The area under the curve (AUC^{0-10} h) of flurbiprofen in FBA emulsion group was 6.7 times higher than that of FBA oil solution group. The nanoparticle with elevated FBA concentration of 0.1% presented a promising NSAID ophthalmic emulsion with low irritancy and improved anti-inflammatory effect.

Liposomes

Liposomes Because of the presence of natural phospholipids, cell-like membrane and excellent

biocompatibility, liposomes are a promising means of delivering ocular drugs. When applied topically, liposomes can attach to the hydrophobic corneal epithelium, where they continuously release the bound drug content, improving pharmacokinetics and decreasing toxic side effects [52] With fluconazole solution as a control, fluconazole-loaded liposome was applied to the rabbit keratits models [53]. After 21 days of observation, results showed that therapy with liposomal fluconazole was successful at eliminating infection and was superior to the control treatment. James M K [90] et al developed an anionic, cholesterol-fusing liposome that can encapsulate minocycline for optimized intraocular drug delivery. These nontoxic nanoliposomes delivered 40% of encapsulated minocycline to the retina after a subconjunctival injection in a diabetes model.

Niosomes

Niosomes are bilayered structural vesicles made up of non-ionic surfactant which are capable of encapsulating both lipophilic and hydrophilic compounds. In a recent approach to deliver cyclopentolate, niosomal formulation was developed It released the drug independent of pH resulting in significant enhancement of ocular bioavailability [54-55].

Niosomal formulation of coated (chitosan or carbopol) timolol maleate exhibited significant Intra Ocular Pressure lowering effect in rabbits as compared to timolol solution. The niosomes of acetazolamide were prepared (by reverse phase evaporation method) and coated with Carbopol for the latter's bioadhesive effect. The developed formulation showed a longer duration of action (6 h with ACZREVbio vis-a-vis 3 h with Dorzox®)[56].

Solid lipid Nano particles

Solid lipid nanoparticles (SLNs) are primarily composed of solid lipids, which thus impart to them some of the fundamental properties of these lipids, including biocompatibility, biodegradability and low-toxicity. SLNs represent a unique class of colloidal drug delivery systems that possess the advantages of both the "soft" drug carriers such as emulsions and liposomes and polymeric nanoparticles. As promising drug carrier systems, SLNs are valuable for nanomedicine and have been widely used as delivery systems mostly for drugs and macromolecules like proteins, oligonucleotides and DNA by various application routes, such as intravenous, oral, duodenalous, intramuscular, pulmonary, intranasal, ocular, rectal and intraperitoneal administrations[57]. Seyfoddin A[58] investigated the ocular bioavailability of acyclovir by incorporating it into solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). This required optimization of the process parameters, such as type of lipid, drug to lipid ratios, type and concentration of surfactants, and type and amount of liquid lipids used in

the formulations. The prepared nanoparticles were spherical and within the size range suitable for ocular drug delivery (400-777.56 nm). The prepared nanoparticles were evaluated for their particle size, zeta potential, entrapment efficiency, solid state characteristics, surface morphology, in vitro drug release, and permeation through excised cornea. The results of the study suggest that SLNs can be successfully converted to physically superior NLCs, which have the potential to be developed further as ocular drug delivery systems for acyclovir. Hippalgaonkar K et al [59] prepared the indomethacin-loaded solid lipid nanoparticles (IN-SLNs; 0.1% w/v) for ocular delivery. Compritol[(®)] 888 ATO was selected as the lipid phase for the IN-SLNs, as indomethacin exhibited a highest distribution coefficient and solubility in this phase. A dramatic increase in the chemical stability and in vitro corneal permeability of indomethacin was observed with the IN-SLN formulation in comparison to the indomethacin solution- (0.1% w/v). Kalam M A et al [60, 61] demonstrated the increased bioavailability of gatifloxacin to the eye using solid-lipid nanoparticles (SLN). The aqueous humor levels of gatifloxacin after single topical instillation in Gate[(®)] Eye drops and positively charged SLN were determined. A 3.37-fold increase in the relative bioavailability was observed with the SLN. The results suggested that SLNs could enhance ocular bioavailability of gatifloxacin and prolong its residence time in the eyes. Moreover, no signs of ocular irritation were seen with the SLN formulations, indicating their relative safety compared to the marketed drops.

Nanosuspensions

Nanosuspenisons usually consist of colloidal carriers like polymeric resins which are inert in nature. They help in enhancement of drug solubility and thus bioavailability.

Unlike microemulsions, they are also popular because of their non irritant nature. Flurbiprofen encapsulated in eudragit RS 100® and RL 100® polymer resins prevents myosis, which might be induced during extracapsular cataract surgery [62] Charge on the surface of nanoparticles facilitates its adhesion to the cornea. Methylprednisolone acetate (MPA) was encapsulated in a copolymer of poly (ethylacrylate, methyl-methacrylate and chlorotrimethyl-ammonioethyl methacrylate) and examined for its effect on the anti-inflammatory symptoms in rabbits with endotoxin-induced uveitis (EIU) [63], Animal studies have revealed that anti-inflammatory effect of nanosuspensions was more than microsuspensions. Similar studies were carried out using piroxicam in eudragit RS 100. In vivo studies in rabbits have shown significant anti-inflammatory effects compared to microsuspensions[64] In another approach, three different types of glucocorticoids; hydrocortisone, prednisolone and dexamethasone were formulated as nanosuspensions. In-vivo study in rabbits suggested that the nanosuspensions significantly

enhanced the ocular absorption of glucocorticoids [65]. These nanosuspensions also produce sustained drug release and were more effective over a longer duration. Katara R and Majumdar D K [91] developed stable Eudragit RL 100-based nanoparticles of aceclofenac of two year shelf life at room temperature. The nanoparticle formulation showed 2-fold higher permeation of drug through excised cornea compared to an aqueous solution of drug with no signs of corneal damage. The in vivo studies involving arachidonic acid-induced ocular inflammation was done in rabbits revealed significantly higher anti inflammatory effect by the nanoparticle formulation compared with the aqueous solution.

Ocular Iontophoresis

Iontophoresis is a noninvasive technique in which a weak electric current is used to drive the penetration of charged molecules into and across percutaneous tissue [66]. By varying the intensity of the electric field, precise amounts of a drug can be delivered relatively specifically to local targets. Iontophoresis has been used in several areas of medicine [67–71], and iontophoresis via the cornea has been in use in ophthalmologic practice and research for many years [72–74].

Numerous iontophoretic devices with different capabilities are commercially available[75-77] .The most basic of these units consist of two electrodes, a power source (battery or AC voltage), timers, and an ampere (A) meter for measuring current output. As iontophoresis is not entirely without risks [72, 78], efforts are continuously made to develop systems that can substantially reduce, if not eliminate, any risk of injury caused by use of the device. The systems discussed below represent a small sampling of those available.

The OcuPhor™ system has been designed, consists of a drug applicator, a dispersive electrode, and an electric iontophoresis dose controller [79-80]. The hydrogel applicator is placed against the sclera in the inferior cul-de-sac, not touching the cornea. A hydrogel dispersive electrode is placed on the right shoulder or right side of the neck to complete the circuit. Both electrodes are connected to the PhoresorR-II PM 700 iontophoresis device (Iomed, Salt Lake City, UT)[72, 76]. Studies have shown that the OcuPhor™ system can deliver therapeutic levels of drugs to both anterior and posterior tissues, including the retina and choroids [82].

A number of antibiotics, including gentamicin, cephazolin, ticarcilin, amikacin and vancomycin have been successfully delivered into the vitreous of rabbit eyes. Transscleral iontophoresis of steroids (dexamethasone and methyl prednisolone), amikacin, gentamicin and other drugs was also reported [83-89]. Regarding safety issues, a continuous assessment of iontophoresis devices, probes, and sites is needed to determine the optimal protocol and conditions for safe and therapeutic use of ocular iontophoresis.

CONCLUSION

Although eye drops represent 90% of all ophthalmic dosage forms, there is a significant effort directed towards new drug delivery systems for ophthalmic administration. It is the consensus of most clinicians that the patient prefers a solution form of ocular drug delivery system provided that extended duration can be accomplished by these forms. Most of the formulation efforts aim at maximizing ocular drug absorption through prolongation of the drug residence time in the cornea and conjunctival sac as well as to slow drug release from the delivery system and minimize precorneal drug loss. The novel drug delivery system like Mucoadhesive, Insitu gel, lipid vesicular systems, nanosuspensions, microemulsions fulfils all the requirements and in addition, it has the advantage of drug to be administered in the form of a drop, which increases patient compliance. In situ ocular drug-loaded nanoemulsion (NE) gels and lipid based nanoparticles are promising drug delivery system that could be employed to improve the pharmacokinetic properties of clearance and distribution in ocular drug delivery to the retina, stress should be given on the formulation optimization, safety and shelf life of the product. In future, much of the emphasis will be given to achieve non-invasive sustained drug release for eye disorders.

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