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GLAUCOMA DRUGS AND THEIR FORMULATION– REVIEW ARTICLE

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ABSTRACT

The leading cause of blindness is glaucoma, a chronic disease characterised by excessive intraocular pressure. For many scholars and formulators, eye delivery has historically been problematic in terms of intricacies of eye anatomy and physiology, generally protecting the eye from hazardous chemicals and preventing the absorption of given eye-drugs at the intended site, resulting in inadequate access for the eye to different sections of the drug. In this article we have compiled few ocular drugs and their formulation which have managed to successfully deliver the drug at the active site and explained briefly along with the recent filing of procedures followed for the same.

INTRODUCTION

Ocular drug delivery has usually been a difficulty for most scientists and formulators related to the complexities of the eye's anatomy and physiology, which generally guard the eye from toxic substances and impede the absorption of administered ophthalmic medications to the desired site of action, resulting in poor drug accessibility to various areas of the eye. The concentration of the medication in the pre-corneal region is the driving force for its passive diffusion across the cornea, hence excellent corneal penetration and prolonged contact time with the cornea are essential for successful drug delivery. A good topical medication formulation improves bioavailability by maintaining drug release and maintaining in touch with the eye for an extended period of time. An ideal ocular medicine delivery mechanism should be created such that it may be provided in the form of eye drops without producing impaired vision or irritation, and that only one or two instillations are required per day. Much of the published evidence suggests that, in the case of ophthalmic drug delivery systems, an optimal particle size and a restricted size range are required to provide minimum irritation, acceptable bioavailability, and tolerability with ocular tissues.[1]

Review of Literature:

Glaucoma, a chronic illness characterised by high intraocular pressure, is the primary cause of blindness. Brimonidine tartrate (BRT), a hydrophilic medication with limited ocular bioavailability, is a three-time-daily glaucoma therapy. Patients' adherence to therapy is hampered by the frequent administration of BRT. The goal of this study is to increase BRT ocular bioavailability and extend its intraocular pressure reducing impact by creating BRT-loaded cubosomes. A d-optimal design was used to create cubosomal formulations.The variables chosen were the percentage of dispersed phase, the glyceryl monooleate to

poloxamer 407 ratio, the type of surfactant, and the surfactant concentration. The drug content, particle size, PDI, zeta potential, and in-vitro release of the produced formulations were all measured. The improved formulation had a size of 157.2 4.2 nm, a PDI of 0.22 0.03, a zeta potential of 30.2 0.6mv, and a 24 h sustained release pattern. Transmission electron micrographs verified the cubic nanostructure of the improved formulation. Ex-vivo corneal permeation demonstrated 1.6 times more permeability than Alphagan®P.[2]

Erodible and thin polymeric films were designed as prospective ocular medication delivery devices to improve bioavailability and provide controlled drug release. Hyaluronic acid (HA) and hydroxypropyl methylcellulose (HPMC), which are presently utilised as thickening agents in eye drops, were used as biocompatible film forming polymers. Two distinct films were created using the solvent casting approach, one as a single polymer and the other as a composite formulation containing glycerol (GLY) as a plasticizer and timolol maleate (TM) as a model glaucoma medication. The formulas were further refined after preliminary optimization for transparency and ease of handling. The formulations were further characterized for their physicochemical properties.

FTIR studies found no evidence of substantial drug-polymer or polymer-polymer (in composite films) interaction, but IR mapping demonstrated homogeneous drug distribution throughout the films. DSC and XRD both verified the amorphization of TM in the film matrix. Swelling tests revealed that HA had a greater swelling capacity than HPMC, which directly altered drug release patterns, making HA a promising polymer for controlled ocular drug delivery. Tensile and mucoadhesion characteristics of HA validated its increased elasticity and adhesiveness, but HPMC created stronger films.

The impact of UV radiation sterilisation on mechanical characteristics was also investigated, and no significant difference was found between sterilised and non-sterilized films. The SEM results validated the smoothness and uniformity of the film surfaces for all formulations tested. In vitro drug dissolution experiments revealed that formulations incorporating HA had longer protracted release characteristics. A cytotoxicity (cell viability) research on HeLa cells using the MTT test indicated that the single polymer and composite films are typically safe for ocular administration. The research revealed that HA and HPMC have strong film forming abilities and can be employed as single polymers or in composite formulations as a viable topical ocular drug delivery platform to improve medication retention on the ocular surface and hence bioavailability.[2]

The formulation of nanosized cubic liquid crystals (cubosomes) as a novel drug carrier system for latanoprost, an anti-glaucoma medication, is presented in this paper. A top-down technique was used to make latanoprost-loaded phytantriol cubosomes (CubLnp). The concentration of latanoprost in the formulations ranged from 0.00125 percent to 0.02 percent by weight. With an encapsulation effectiveness of roughly 90%, all cubosomes had an average size of approximately 200 nm, a low polydispersity index of 0.1, and zeta potential values of –25 mV. Drug loading had no effect on the structure of cubosomes, which had a double-diamond surface and a Pn3m cubic-phase structure. Calorimetric tests demonstrated that latanoprost and cubosomes interact quickly and exothermically. Latanoprost release from cubosomes was gradual in time, indicating a prolonged release profile, according to in vitro analyses. CubLnp was administered subconjunctivally to normotensive rabbits to assess the in vivo hypotensive intraocular impact based on this behaviour. In contrast to a commercially available latanoprost formulation (0.005% w/v), promising results were found.[4]

Glaucoma is the most common cause of permanent blindness in the globe. Although latanoprost is one of the most efficient medications for glaucoma therapy, it requires frequent administration, which leads to poor patient compliance. The goal of this study was to create a patient-friendly

niosome-in-gel method for latanoprost ocular administration. Glaucoma is the leading cause of irreversible blindness worldwide. Despite the fact that latanoprost is one of the most effective glaucoma treatments, it needs frequent administration, which leads to poor patient compliance. The purpose of this research was to develop a patient-friendly niosome-in-gel technique for ocular delivery of latanoprost. As a result of these findings, FT-IR experiments revealed nonspecific interactions between latanoprost and various niosomal components, resulting in an encapsulation efficiency of 88 percent. The drug/surfactant ratio boosted the encapsulation efficiency of latanoprost, and encapsulation efficiency of 98 percent was achieved at a ratio of 50 percent. Pluronic® F127 was the most effective in maintaining drug release from niosomes. This gel had no harmful or irritating effects on rabbit eyes and decreased intraocular pressure for three days, which was substantially longer than commercial latanoprost eye drops.[5]

Brinzolamide (BNZ) is a carbonic anhydrase inhibitor that is often used for glaucoma therapy. In a research, BNZ-loaded chitosan-pectin mucoadhesive nanocapsules (CPNCs) were produced for ocular distribution using the polyelectrolyte complex coacervation technique and their anti-glaucoma effectiveness was assessed. In-vitro and ex-vivo release of the produced CPNCs was evaluated for particle size, polydispersity index, zeta-potential, surface morphology, entrapment efficiency, drug loading efficiency, and mucoadhesive strength. On a glaucoma-induced rabbit eye model, pharmacodynamic tests for CPNCs were undertaken and compared to the marketed medication. All of the formulated CPNCs had a size range of 217.01 0.21 to 240.05 0.08 nm, as well as suitable physico-chemical characteristics, and showed BNZ erosion-diffusion release during an 8-hour period. According to an ex-vivo corneal permeation research, BNZ loaded CPNCs permeate the cornea at a possibly greater rate than the marketed product. In a pharmacodynamic research, CPNCs had a stronger impact on decreasing intraocular pressure than the marketed pharmacological product. The study found that CPNCs are a viable alternative to traditional eye drops because of their capacity to increase bioavailability through a prolonged precorneal retention period and prolonged medication release.[6]

The goal of this study was to see if niosomal gels filled with the cholinergic medication pilocarpine HCl may help with glaucoma therapy by extending precorneal residence time and increasing bioavailability. Pilocarpine HCl niosomes were made by ether injection utilising several nonionic surfactants (span 20, span 60, and span 80) in the presence of cholesterol at varied molar ratios. Carbopol 934 and locust bean gum-based gels were used to include the chosen formulations. The niosomes generated were spherical in shape and had a distinct interior aqueous space with uniform particle size, according to TEM examination.

Among the other formulations, Formulation F4 with span 60 and cholesterol (1:1) had the highest entrapment (93.26 1.75 percent) and the slowest release (Q8h = 60.35 1.87 percent). In-vitro drug permeation tests revealed that niosomal gels released drug for a longer time than niosomes themselves. In terms of in-vitro drug release, the niosomal gel formulation G2 was the best of the formulations tested. The data from the release were fitted to an empirical equation, indicating that the release is governed by a non-Fickian diffusion process. The integration of niosomes in gel boosted their stability more than the niosome itself, according to the stability research. Draize's test revealed no symptoms of redness, inflammation, edoema, or increased tear production for the tested formulation during the research period. The relative bioavailability of the G2 formulation for decreasing intraocular pressure (IOP) was 2.64 times that of the commercialised Pilopine HS® gel. These findings showed that niosomal gels containing pilocarpine HCl might be useful as ocular carriers in the treatment of glaucoma.[7]

The use of acetazolamide-loaded nano-liposomes and hydroxypropyl

methylcellulose (HPMC) in an osmoprotectant medium (trehalose and erythritol) to boost the ocular bioavailability of poorly soluble medicines is presented as a new method. Ophthalmic formulations based on acetazolamide-loaded liposomes dispersed in osmoprotectant solution (ACZ-LP) or in conjunction with HPMC (ACZ-LP-P) were described and tested in vivo. Both formulations produced physiological ranges due to their pH and tonicity. The addition of HPMC increased viscosity (from 0.9 to 4.7 mPas), and 64.9 2.6 percent of the acetazolamide in the formulation was retained in the vesicles. After a single instillation (25L) in the eyes of normotensive rabbits, both formulations had a similar onset time (1 h) and effective time period (7 h). The ACZ-LP-P had a 1.5-fold greater AUC0–8h than the ACZ-LP (p 0.001) and a 1.4-fold greater maximal hypotensive effect (p 0.001). In addition, as compared to the drug solution, the formulation of ACZ in the hybrid liposome/HPMC system resulted in a 30.25-fold increase in overall ocular bioavailability. The study confirmed an excellent tolerance in rabbits' eyes.[8].
Hydrophilic medication eye drops are routinely used in patients with glaucoma to lower intraocular pressure (IOPs), however compliance with therapy is often diminished via frequent dose and eventual systematic adverse effects. Sustained-release drug delivery methods, such as ocular inserts, can help patients adhere to therapy by reducing dose, limiting systemic exposure, reducing side effects, and reducing adverse effects. We created and tested ocular inserts made of chitosan/hydroxyethyl cellulose for the long-term release of dorzolamide, a hydrophilic medication.

The solvent-casting methods for inserts with dorzolamide (DI) were used, characterised by different physical chemicals. Studies of pharmacokinetics were conducted with scintigraphic and ex vivo biodiversity pictures. In glaucomatous rats the efficacy of inserts was investigated. Characterization investigations indicated the drug reacted significantly with the polymer matrix, however DI required just 3 hours for release of 75% of the dorzolamide caught. However, scintigraphic pictures and ex vivo bio distribution investigations showed that after 18 h of administration of DI, more than 50% of the 99mTc-dorzolamide stayed in the eye, whereas only around 30% remained eye-after-drop instances. For two weeks after single treatment DI had a substantial hypotensive impact, while placebo and unprocessed groups still had elevated IOP values. Only during the therapy time were eye drops effective. The retinal ganglion cells died only with diabetes medication. These results have shown that polymer inserts may be used to control glaucoma continuously for dorzolamide.[9]

A study targeted at developing brimonidine tartrate-loading of poly(lactic-co-glycolic acid) nanoparticles in thermo sensitive in situ gel for the development of E-tocopheryl polyethylene glycol 1000 sucinate, in order to enhance mucoadtensive characteristics and drug retaining capabilities for better glaucoma management. Using box-behnken design, nanoparticles were optimised (BBD). Different PLGA (0.1–0.4% w/v) and TPGS (0.3–0.5% w/v) were used in the preparation of the formulations. Fourier infrarspectroscopy analysis (FTIR), differential calorimetry scanning (DSC) and transmitting electron microscopy (TEM), demonstrated compatibility with the drug excipient and validated the compatibility of nanoparticle.

Transcorneal permeability, gelation duration, gelling temperature, and rheological experiments were all performed on the nanoparticles integrated gel. In addition, in vitro, intraocular pressure (IOP) and medication release tests were done for improved gel. In a rabbit model, the biocompatibility of formulations was studied. The mean size, polydispersity index (PDI), zeta potential, and entrapment efficiency (percent EE) of the drug-loaded nanoparticles were 115.72 4.18 nm, 0.190 0.02, 11.80 2.24 mV, and 74.85 6.54 percent, respectively. The sustained and continuous release BRT release from Poloxamer-based in situ gel was 85.31 3.51 percent till 24 hours, compared to marketed

eye drops. At 4 hours, the optimised in situ gel's transcorneal steady-state flow (136.32 g cm2 h1) was roughly 3.5 times greater than the marketed formulation's (38.60 g cm2 h1) flux. Until 8 hours, the improved formulation has a threefold larger impact on percentage decrease of IOP (34.46 4.21%) than the commercial formulation (12.24 2.90%). The inclusion of optimised BRT-PLGA-TPGS nanoparticles into a thermosensitive in situ gel matrix to increase precorneal residence duration without causing eye discomfort, as well as the continuous release of BRT through the cornea for successful glaucoma therapy.[10]

Because a considerable amount of the intended dose is lost through eye drainage quickly after application, traditional eyedrops routinely employed to provide ophthalmologic therapies do not provide a sustained administration of the medicine. For application in ocular medication administration, a micrometric-sized crosslink gel based on copolymers integrating thermal-sensitive copolymers was suggested. For in vitro study of ocular medication release, eyedrops based on a thermo responsive polymer were created by combining poly(acrylic acid-graft-N-isopropylacrylamide) (PAAc-graft-PNIPAAm) with PAAc-co-PNIPAAm gel and adding [3H]-epinephrine.

Eyedrops are transparent solutions at room temperature, but when they come into contact with the ocular surface, they partially solidify into a soft thin coating. When the in vitro release kinetics of embedded [3H]-epinephrine were evaluated, PAAc-graft-PNIPAAm was shown to have a quicker drug release profile, however a combination of PAAc-graft-PNIPAAm and PAAc-co-PNIPAAm gel had a more prolonged release profile, indicating that the anomalous transport mechanism is a crucial feature. Treatment of epinephrine in polymeric eyedrops substantially decreased intraocular pressure (IOP) for 36 hours, which is a significant extension of the impact compared to the 8-hour IOP decrease reported following administration via conventional eyedrops. Overall, our findings show that the kinetics of drug release from polymeric eyedrops are influenced by crosslinking density, which influences the creation of capillary networks in the polymer matrix and hence governs drug diffusion into the polymeric network, making this a viable method to controlled drug release in ocular drug delivery.[11]

Glaucoma is the most common cause of persistent visual loss. However, currently available popular treatment approaches, such as eye drops, have a number of drawbacks, including patient noncompliance owing to repetitive administration and low (1–5%) absorption, resulting in low efficiency. The goal of this study was to create Eudragit-based levobunolol nanoparticles that could be put into a contact lens to achieve long-term ocular administration of levobunolol at the therapeutic level. Nanoprecipitation was used to create Eudragit nanoparticles of levobunolol using varied ratios of Eudragit S100 and polyvinyl alcohol. Formulation F3 was created as an optimised nanoparticle formulation with a particle size of 102.61 nm 3.92, a zeta potential of 22.2 mV 2.76, and an entrapment effectiveness of 86.995 percent 1.902. When compared to medication solution-loaded lenses, the equilibrium swelling index and transmittance of nanoparticle put into contact lenses revealed better results. When compared to drug solution-loaded lenses (89.282 percent 0.900 of drug release over a period of 3 days), in vitro release revealed higher sustained drug profiles (84.33 percent 0.34 of drug release over a period of 12 days). When compared to marketed eyewear, ex vivo transcorneal permeation experiments revealed greater permeability (6.75 percent 0.170) via contact lenses as compared to marketed eye drops (3.03% ± 0.088). This study illustrates the extraordinary outcomes of drug-loaded contact lenses as a fantastic medium for the ongoing administration of ocular medications without compromising the lens content's physical and optical properties.[12]

A three-dimensional structured hydrogel-based formulation was used to make an effort. The goal of this project was to design, develop, and characterise a Timolol hydrogel formulation for glaucoma with a

low dosage of 0.1 percent timolol to obtain maximal therapeutic response over a long period of time. The raw drug Timolol maleate, gellan gum, chitosan, PLGA, and other materials of analytical quality were employed in this investigation. Timolol hydrogel was made using the cold condensation process. Different characteristics such as release pattern, viscosity, pH, permeability, and sterility were used to evaluate the prepared hydrogel. In comparison to its convectional dose form, timolol maleate in hydrogel formulation has a steady and increased bioavailability. It was discovered that using a hydrogel increases the amount of time the medicine stays in touch with the eye after being administered, as well as the length of drug release from the formulation, without causing irritation or adverse effects. Timolol maleate in a hydrogel formulation has several advantages over the current formulation, including the need for a lower dosage of 0.1 percent Timolol maleate in a single administration. Among the current formulations on the market, this attempt at hydrogel formulation would be clearly useful with suitable lower doses and maximal therapeutic effects.[13]

In order to minimise dose frequency and improve patient adherence, effective glaucoma pharmacotherapy relies on treatments that lower intraocular pressure (IOP) and keep the IOP lowering effect for a long time. Therefore a promising treatment method may consist of combined anti-glaucoma treatment and dose forms that enhance precorneal residency periods. Self-assorting peptide ac-(RADA)4-CONH2 in situ gel was assessed as a carrier for the co-alimentation between timolol maleate (TM) (BR). The microstructure and mechanical characteristics of the hydrogel were evaluated using atomic force microscopy and rheology, respectively. The diffusion of hydrogel drugs was studied ex vivo, via porcine cornea in simulated tear fluid in vitro. The results showed that co-delivery of TM and BR altered the microstructure of the hydrogel, resulting in shorter nanofibers and a less stiff hydrogel matrix. Both medicines were released rapidly and completely within 8 hours, with TM and BR having 2.8-fold and 5.4-fold greater corneal permeability, respectively. The structural integrity of the corneas treated with the hydrogel formulation was not significantly altered. The automatically assembled peptide hydrogels might be a viable technology for antiglaucoma combo treatment.[14]

The goal of the study was to create a stable formulation and manufacturing method for a fixed dosage antiglaucoma medication (BTD) including brimonidine tartrate, timolol maleate, and dorzolamide hydrochloride. An investigation of their description, pH and assays utilising equipment such as a pH metre and high-performance liquid chromagraphy were examined by compatibility studied with product contact materials such as platinum-curated silicone tube, SS 316L (metal) and nylon membrane filter (HPLC). The outcomes of the formulas were evaluated, and they were determined to be well within the stipulated limitations. The BTD formulation was made by dissolving all of the components in water for injection while stirring constantly, and then filtering the solution through a sterilised 1.2 nylon pre-filter and a 0.2 nylon filter. Conclusion: A compatibility study was conducted to assess the physical and chemical stability of the BTD formulation, and the results show that it is physically and chemically stable.[15]

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