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Research Article

VESICULAR CARRIER LOADED IN-SITU THIXOTROPIC FORMULATIONS FOR GLAUCOMA: AN OVERVIEW OF RECENT ADVANCEMENT IN OCULAR DRUG DELIVERY SYSTEM

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ABSTRACT

Objective : The primary objective of this study is to investigate the approaches for ophthalmic formulations which successfully can overcome the various anatomical and physiological barriers thus ensuring an enhancement in drug permeability and efficacy. The exploration also establishes role of in situ gels as an effective formulation concept to resolve the ongoing complications. **Conclusion:** The pharmacodynamic and pharmacokinetic studies under investigation showed an enhanced efficacy compared to conventional eye drops. Acetazolamide in situ formulation showed 2.29 fold more effective than Azopt, 2.37 fold more effective than cimdaex. In situ gel of timolol maleate was able to lower down the elevated IOP from 15.73 mm Hg – 17.73 mm Hg over course of 30 – 300 minutes and latanoprost in situ gel was effective for a sustained time interval of 72hr with compared to 24hr of Xalatan drop characterized by a decrease in IOP to the baseline.

Keywords: Ophthalmic, in situ gel, acetazolamide, timolol maleate, latanoprost, IOP.

INTRODUCTION

Glaucoma, a disorder designated by increased intraocular pressure leading to injury of the optic nerve is a mainstream cause for temporary vision loss [1]. Innumerable orthodox approaches for drug delivery are developed as solutions and suspensions in the form of eye drops. Nevertheless, the management of glaucoma has been a defacing affair for health care professionals. It is owing to the verity that the patient adherence to the medication is been miserable. Due to in compliance with the dosing regimen, more than 70% of patients have been discouraged for coherence to the medication until the disease gets managed and consequently, re-medication is required to resolve the enigma [2]. This paramount financial oppression on patients. Further, among the patients who are adhered to proper medication, less than 5 % of the drug reaches the action site**,** Remaining 95% of drugs either gets drained by tear, as well as are unable to cross the various biological barriers present in the anatomical sections of the eye [1, 3]. Overall, the ocular bioavailability of the drug becomes eminently minimal. Any bid to increase ocular bioavailability by amplifying the dose, however, leads to severe adverse effects and toxicity progenies.

An array of research was carried out for the alternative dosages using novel formulations includes vesicular carriers as well as thixotropic gels. Amidst vesicular carrier system, drug, when loaded in formulations like Liposomes, Niosomes, Ethoniosomes, Spanlastics, Nano lipid carriers, Microspheres, and Nanoemulsions, exhibited profound enhancement in their approach of physiological barrier penetration [2, 5]. As a result overall bioavailability was increased. It is primarily considering the configurational arrangement of the structural constituent of vesicles, which felicitates the drug with obligatory attributes to penetrate across the barriers. Another approach is the development of in-situ thixotropic gels, where drugs are incorporated in a low viscous polymeric solution which upon installation in the eye undergoes physiological transformation leading to the constitution of a clear viscous gel that resides locally overcoming the lachrymal washout of the active drug molecules [4, 5]. It thereby increases the contact time of drug to the cornea and thereby improving the bioavailability of the system.

Besides, vesicular carrier systems get effortlessly drained by the tear because of its low consistency, resulting in the poor contact time and the overall objectives exhibit shortcomings. Correspondingly, the in-situ gels although it provides the required contact time but fails to influence on the penetration essence of the drug. Interestingly, the vesicular systems possess the key to unlock the in-situ gel deficiencies in the same way gel posses the answers to vesicular system insufficiencies. These two formulations on a coalition complement each other and thus overcomes the individual deficiencies making the prospect an effectual as well as fecund [7, 8] Recently, plenteous exploration in the domain of vesicular carrier loaded in-situ gel is going through owing to its superiority. The varied active pharmaceutical ingredient is capable of inducing potent therapeutic value in order to minimize the intraocular pressure. These include the likes of beta-blockers, carbonic anhydrase inhibitors, alpha adrenergic agonist, cholinergic agents as well as hyperosmotic agents [5, 6]. Several investigations have been carried out in this theme. Among, the best possible outcomes are adopted by the manufacturers and the wholesome of research is still been conducted for further advancement.

Some of the formulations approved by **the FDA** are enlisted in the below table 1. [6]

Table 1: Formulations Approved By FDA

Name	Composition	Class	Dosage	Manufacturer
TIMOPTIC XE	Timolol maleate 0.25 %, 0.5%	Beta-blocker	Ophthalmic Solution	Merck
ISTALOL	Timolol maleate 0.5%	Beta-blocker	Ophthalmic Solution	ISTA
BETOPIC	Betaxolol HCl 0.25%	Beta-blocker	Ophthalmic Solution	Alcon
IOPIDINE	Apraclonidine 1.0%	Alpha adrenergic agonist	Ophthalmic Solution	Alcon
ALPHAGAN	Brimonidine tartrate 0.2%	Alpha-adrenergic agonist	Ophthalmic Solution	Allergan
ALPHAGAN P	Brimonidine tartrate 0.1, 0.15%	Alpha-adrenergic agonist	Ophthalmic Solution	Allergan
TRUSOPT	Dorzolamide 2%	Carbonic anhydrase inhibitor	Ophthalmic Solution	Merck
AZOPT	Brinzolamide HCl 1%	Carbonic anhydrase inhibitor	Ophthalmic Solution	Alcon

DIAMOX	Acetazolamide 500mg	Carbonic anhydrase inhibitor	Oral pills	Sigma
NEPTAZANE	Methazolamide 25 mg, 50 mg	Carbonic anhydrase inhibitor	Oral pills	Wyeth & Ayerst
DARANIDE	Dichlorphenamide 50 mg	Carbonic anhydrase inhibitor	Oral pills	Merck, Sharp & Dohme
COSOPT	Dorzolamide HCl 2%, timolol maleate 0.5%	Fixed drug composition	Ophthalmic Solution	Merck
COMBIGAN	Brimonidine tartrate 0.2%, timolol maleate 0.5%	Fixed drug composition	Ophthalmic Solution	Allergan
DUOTRAV	Travoprost 0.004%, timolol maleate 0.5%	Fixed drug composition	Ophthalmic Solution	Alcon
SIMBRINZA	Brinzolamide 1% brimonidine 2 %	Fixed drug composition	Ophthalmic Solution	Alcon
Zioptan	Tafluprost	Prostaglandin analogues	Ophthalmic Solution	Merck
Vyzulta	Lanoprostene	Prostaglandin analogs	Ophthalmic Solution	Bausch & Lomb
Rhopressa	2017 November 2017 December	Rock inhibitor	Ophthalmic Solution	AeriePharmaceuticals

RECENT PROGRESS

Emulsion-based gel

Nadia Morsi et. al devised Nano-emulsion based electrolyte triggered in situ gel for acetazolamide, a cogent remedy accompanying carbonic anhydrase inhibitor portrayed by significant reduction in elevated intraocular pressure (30%), barring substandard aqueous solubility (0.7 mg/ ml) , inferior penetration coefficient (4.1 * 10 ^ - 6) and prompt washout by tear fluid when fabricated conventionally. The intent of the aforementioned investigation was to design a Nanoemulsion (o/w) which provides the high solubilizing capacity of drug, amplify drug penetration to the active sites, extend the contract period of a drug to the corneal membrane by improving the drug coalition with precorneal film constituents. The research additionally illustrated an objective to explore the benefit of incorporating surfactant and co-surfactant combination to draw the remarks on solubility and permeation characteristics. Six pseudo-ternary systems consisting Peanut Oil, Surfactant (Tween 80 & cremophor EL 1:1), Co surfactant (Polyethylene glycol and Transcutol P) were fabricated using water titration method at 25^{o}C. Surfactant /co-surfactant: oil ratio at 9.5: 0.5 at 60% water content was selected to be loaded with acetazolamide. 1% w/w of acetazolamide was sonicated with blended surfactant/co-surfactant, oil until complete dissolution of the drug molecule. The dropwise addition of the aqueous phase into the blend is done concurrently. Gellan gum taken to prepare concentrations 0.1 %, 0.2%, 0.3%, 0.4%, 0.5%, 0.6 % by utilizing 5% of water content from Nanoemulsion mixed at 90^{o}C for 20 minutes. Also gellan gum 3.0% in addition with xanthan gum, HPMC K4M, Carbopol 940 at concentrations 0.2%, 0.4%, 0.6% were prepared and pH was adjusted to 5.4 – 5.7. The Nanoemulsion was of 11-15 nm size and were clear transparent which was characterized by the refractive index i.e. 1.34 – 1.36 (close to tear), however, the transparency reduced by 15% on gelation. The gel exhibited shear thinning pseudoplastic flow in physiological as well as non-physiological condition, also the viscosity was found to be in the range of 36.7 – 87.5 cp of as many formulations. The gel of gellan gum alone was least viscous among all formulation followed by the combination of gellan gum and HPMC, gellan gum and Carbopol, gellan gum and xanthan gum. Gellan gum of 0.3% concentration illustrated the gel strength in range 29-41. Gel strength between 25 to 50 exhibits high release and low surface tension. In vitro studies demonstrated an 80 % release in 3 hrs for Nanoemulsion following the Higuchi model release which decreased by 2 folds while carried out for gel. Gellan gum and xanthan gum combination gel were evident for the slowest release among all. The formulations were subjected to stability testing where each formulation was exposed to 40, 25 and 4 for the course of 3 months. The formulation containing Carbopol exhibited instability due to incompatibility with the drug, while all other formulations were profoundly stable7. The pharmacodynamic studies were carried out by testing the level of drug responses in albino rabbits and the results were compared comprehensively with the marketed formulation of Azopt drop and cidamex tablets containing brinzolamide as the active pharmaceutical ingredient which has higher intrinsic permeability with regard to acetazolamide used for the test formulation. The results reflected degree of treatment as F2> F5>Azopt > cidamex for [AUC] 0→10 . Also, the formulation F2 (gellan gum 0.3% and xanthan gum 0.2%) was 2.29 fold more effective than Azopt, 2.37 fold more effective than cidamex. Formulation F5 (0.3% gellan gum and 0.2% HPMC K4M)also showed 1.77 fold activity compared to Azopt and 1.83 fold activity to Cidamex.

Liposome-based gel

Shi Hui yu et. al**,** in 2015 prepared liposome incorporated ion sensitive gel for ophthalmic delivery of timolol maleate. The approach was to increase ocular bioavailability and increase patient compliance. Vesicles were prepared by the pH gradient method coupled with reverse phase evaporation, where phosphatidylcholine and cholesterol in ratio 8 : 3 dissolved in ether constituting the drug-loaded oil in water emulsion portion. The solvent was evaporated at 40 Celsius and then osmotically regulated by using mannitol and pH adjusted by tris HCl buffer to 9.2 setting up the transmembrane pH gradient. The coarse emulsion is then subjected to probe ultrasonic cell disruptor for three minutes followed by the addition of mannitol to regulate osmolarity in 260-330 mOsm and the final pH is adjusted to 7.0. The gel of deacetylated gellan gum was prepared of 0.2%,0.4%, 0.6% and finally the liposomes were incorporated into the gel adjusting the final concentration of timolol maleate 0.25% w/v. The formulation was subjected for particle size analysis and TEM studies where uniform, dark solid at the core, spherical dual-layered vesicles of size range 136nm were characterized. The permeation studies concluded that a 1.93-degree increase in permeation coefficient when compared to eye drop, also the trans corneal drug concentration of drug was found to be 2 fold higher when correlated to the eye drop. The formulation containing 0.4% DGG showed good retention time and viscosity when studied for 30 hours in vivo. The fluorescence imaging studies reflected that the gel had prolonged retention time than that of a drop. No irritation signs were observed when in vivo studies were performed for shorter and longer periods of time. The pharmacodynamic studies were performed on albino rabbits and the effect of test formulation was able to lower down the elevated IOP from 15.73 mm Hg – 17.73 mm Hg hypertensive stage, to 11.96 mm Hg over course of 30 – 300 minutes, comparatively the eye drops lowered down the IOP to 13.61 mm Hg in 30 - 180 minutes.

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Fabricated a liposomal in situ gel of latanoprost using both film hydration and reverse phase evaporation technique and followed by incorporation of different gelling agents as Carbopol 934 0.5%w/w, Pluronic F 127 20%w/w, HPMC 2% w/w where the final drug concentration was 0.005%w/w. The vesicles were characterized by 0.99 to 1.30 µm, large core without aggregation smooth surface and uniform size. In vitro studies showed a 40% drug release from liposomes in which 30% drug was only dispersed into a gel for the course of 24 hours. The rate-limiting step for the drug release was established that the bilayer penetration was extensively an important step, also the formulation reflected the Higuchi model of drug release. The in vivo studies revealed maximum reduction in IOP after 4 hours of

administration in test formulation. After 6 hr of administration, the gel was more consistently lowering the IOP than the marketed Xalatan drop. The test formulation was effective for a sustained time interval of 72hr with compared to 24hr of Xalatan drop characterized by a decrease in IOP to the baseline.

CONCLUSION AND FUTURE ASPECTS

Vesicles based in situ gels have been an encouraging approach for the formulators to incorporate drugs having low permeability across the congested anatomic of the eye. Also, the environmental barriers as the likes of lachrymal drainage is a mainstream cause of ineffective of conventional and low viscous formulations. In these cases, the choice of formulation becomes an integral part of the medication program and thus vesicles loaded in situ gel becomes an appropriate answer for the ongoing crisis. vesicles provide the drug better surface acting properties, size and charge which uplifts the penetrative action of the drug. Gels, however, strengthens the flow property of formulation enabling them to reside for a longer time at the site of action thus up folding the flux of drug. The in situ gel approach improves the homogeneity of formulation and also encourages the compliance on application. The overall effect becomes enhanced drug influx to action site for sustained period summarizing the end advantages as improved bioavailability and patience compliance in regard to dosing regimen and application. The same approaches can be adapted for other disorders where the formulations are unable to act effectively by the curse of anatomical barriers and compromised physical properties of drugs.

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