Chapter - 3

3. Literature Review

All knowledge that the world has ever received comes from the mind; the infinite library of the universe is in our own mind

– Swami Vivekananda
Literature Review

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3. Literature Review

3.1. Review of work done on Olopatadine HCl – Ocular drug delivery

Hampel FC Jr et al\(^1\) studied and evaluated the effect of a new nasal antihistamine, olopatadine, on patients. Olopatadine nasal spray was an effective antiallergy medication that significantly improves the QoL of patients suffering from SAR.

Avunduk AM\(^2\) studied and compared the clinical efficacy of topical ketotifen and olopatadine eye drops and to determine the effects of these 2 drugs on the expression of cell adhesion molecules (CAMs) and inflammatory markers in conjunctival surface cells in patients with SAC. Both active treatments were more efficacious compared with artificial tear substitutes and were well tolerated.

Nickels AS et al\(^3\) formed from a comprehensive literature search with information taken from meta-analyses, systematic reviews, treatment guidelines and clinical studies on children and adults. Articles that have been selected evaluate the use of intranasal and ocular antihistamines and their role in allergic rhinitis and conjunctivitis. Olopatadine is a viable alternative and addition to the mainstay therapy of these conditions with intranasal steroids and oral antihistamines. The compliance of the patients would be improved if a once-per-day formulation of olopatadine was developed for intranasal/ocular application.

Kaliner MA et al\(^4\) Olopatadine is a tricyclic compound with antihistaminic, mast cell-stabilizing, and anti-inflammatory properties. In the United States olopatadine is approved as a twice day ophthalmic solution, Patanol (Alcon Laboratories, Inc., Fort Worth, TX) to treat all signs and symptoms of allergic conjunctivitis and as a once day formulation, Pataday (Alcon Laboratories, Inc.), to treat itching associated with allergic conjunctivitis. Data support consideration of nasal olopatadine for as-needed use for episodic symptoms of allergic rhinitis, for treatment of nonallergic rhinitis,
conjunctivitis and for use in combination with topical steroids for patients with moderate-to-severe allergy symptoms.

Uchio E et al: In a conjunctival allergen challenge (CAC) test, olopatadine hydrochloride 0.1% ophthalmic solution significantly suppressed ocular itching and hyperemia compared with levocabastine hydrochloride 0.05% ophthalmic solution, and the number of patients who complained of ocular discomfort was lower in the olopatadine group than in the levocabastine group. It was expected that olopatadine hydrochloride ophthalmic solutions may be used in patients with a more severe spectrum of allergic conjunctival diseases, such as vernal keratoconjunctivitis or atopic keratoconjunctivitis, in the near future.

Abelson MB made comprehensive description of the pharmacology of the olopatadine molecule, as well as of the clinical efficacy, tolerability, and safety of olopatadine 0.2% ophthalmic solution. Olopatadine 0.2% was found to be a safe and effective medication for the reduction of itching with duration of action of up to 24 h. The added convenience of a once-a-day dosing regimen is a major advancement in this drug class.

Abelson MB et al Olopatadine 0.1% (Patanol) and olopatadine 0.2% (Pataday) ophthalmic solutions are topical ocular anti-allergic agents with antihistaminic and mast cell stabilizing properties. The efficacy of two doses of olopatadine 0.1% was compared to one dose of olopatadine 0.2% in the prevention of ocular itching associated with allergic conjunctivitis over 24 hours. Both showed significant activity at the 24-hour time point and were statistically superior to placebo. No adverse events occurred while on drug therapy.

Berger WE et al: Olopatadine hydrochloride ophthalmic solution 0.2% is a new once-daily formulation of olopatadine that is indicated for the treatment of ocular itching associated with allergic conjunctivitis. This formulation had demonstrated a safety, efficacy and comfort profile similar to that of olopatadine 0.1%.
3.2. Review of work done on Doxycycline hyclate —
Periodontal drug delivery

Javali MA et al. conducted a randomized crossover split mouth design for, a total number of 130 sites from 4 patients, 63 sites from patients with aggressive periodontitis and 67 sites from chronic periodontitis patients were selected. In 90 days study, all the three groups showed significant reduction in clinical parameters. But on comparison, SRP and doxycycline group showed better results than doxycycline alone group and SRP alone group. The results of this study demonstrated that doxycycline hyclate 10% gel (Atridox) is as effective as SRP in reducing the clinical signs of periodontitis.

Paquette DW et al. indicated that locally administered antimicrobials may enhance the effects of periodontal surgical therapy and may reduce the signs of peri-implantitis. The consistency of these findings supports the use of locally administered antimicrobials for managing dental patients with chronic periodontitis.

Gupta R et al. evaluated and compared the efficacy of subgingivally delivered 10% doxycycline hyclate and xanthan based chlorhexidine gels when used as an adjunct to scaling and root planing (SRP) in the treatment of chronic periodontitis. The results suggested treatment with 10% doxycycline hyclate and xanthan based chlorhexidine gels as an adjunct to SRP improves PPD and CAL patients with periodontitis compared to SRP alone. The use of local drug therapy may refocus the need for surgical periodontal therapy toward deeper pockets.

Drisko CH: The clinical safety and effectiveness of a subgingivally delivered biodegradable drug delivery system containing doxycycline hyclate (DH) has been evaluated in 3 large 9-month multicenter randomized parallel-design controlled clinical trials. Results of these 3 large clinical trials demonstrated that treatment of periodontitis with 10% doxycycline hyclate in a bioabsorbable delivery system is equally as effective as SRP and superior in effect to VC and OH in reducing the clinical signs of adult periodontitis.
Bogle G. et al\textsuperscript{13} discussed the perspective of a private practice clinician who participated in the phase III clinical trials of Atridox (doxycycline hyclate) 10%. Atridox may be used either before or after scaling and root planing or, in more rare circumstances, as a stand-alone therapy.

Johnson LR\textsuperscript{14} reviewed the studies that provided the safety and efficacy data essential for the Food and Drug Administration approval of Atridox. These studies detail the clinical effectiveness of Atridox and provide the foundation for an understanding of the use of Atridox in the clinical management of patients with periodontitis. Atridox is a locally delivered, controlled-release system for the administration of high concentrations of doxycycline to the periodontal pocket. Nine-month clinical studies involving more than 800 patients have shown Atridox and scaling and root planing to be superior to placebo and oral hygiene for the efficacy parameters of attachment level, probing depth, and bleeding on probing.

Johnson LR\textsuperscript{15} examined the clinical outcomes of treatment with locally delivered controlled-release doxycycline or scaling and root planing (SRP) in subsets of adult periodontitis patients with known baseline levels of subgingival calculus. Treatment with either doxycycline or SRP resulted in significant statistical and clinical improvements in condition.

Garrett S et al\textsuperscript{16} report evaluates clinical changes resulting from local delivery of doxycycline hyclate or traditional scaling and root planing (SRP) in a group of patients undergoing supportive periodontal therapy (SPT). Results show that both without concomitant mechanical instrumentation and SRP were equally effective as SPT in this patient group over the 9-month study period.

Phaechamud T et al\textsuperscript{17} developed and characterized the chitosan sponges loading with doxycycline hyclate and their antibacterial activities. Sustainable antibacterial activity of developed sponge was evident against S. aureus and E. coli. In conclusion, the \textit{in vitro} release profile and antibacterial efficiency indicated that doxycycline hyclate could be sustained using chitosan sponge.
3.3. Review of work done on Ocular in situ gelling systems utilizing

3.3.1. Gellan gum (Gelrite)

Patel LD et al. developed an optimized thermoreversible in situ gelling ophthalmic drug delivery system based on Pluronic F 127, containing moxifloxacin hydrochloride as a model drug. A $3^2$ full factorial design was employed with two polymers: Pluronic F 68 and Gelrite as independent variables used in combination with Pluronic F 127. Gelrite loading showed a positive effect on bioadhesion force and gel strength and was also found helpful in controlling the release rate of the drug.

Liu Y et al. developed an ion-activated in situ gelling vehicle for ophthalmic delivery of matrine. The rheological properties of polymer solutions, including Gelrite, alginate, and Gelrite/alginate solution, were evaluated. In addition, the effect of formulation characteristics on in vitro release and in vivo precorneal drug kinetic of matrine was investigated. On the basis of the in vitro results, the Gelrite formulations of matrine-containing alginate released the drug most slowly. Both the in vitro release and in vivo pharmacological studies indicated that the Gelrite/alginate solution had the better ability to retain drug than the Gelrite or alginate solutions alone. The overall results of this study revealed that the Gelrite/alginate mixture can be used as an in situ gelling vehicle to enhance ocular retention.

Gupta H et al. described the formulation and evaluation of chitosan and gellan gum based novel in-situ gel system activated by dual physiological mechanisms. Chitosan (a pH-sensitive polymer) in combination with gellan gum (an ion-activated polymer) were used as gelling agent. Timolol maleate, the drug which is frequently used for glaucoma therapy was used as model drug to check the efficacy of the formulation.

Kador PF et al. investigated whether increasing the viscosity of a topical aldose reductase inhibitor suspension increases the lenticular bioavailability of the inhibitor.
and whether such a formulation can arrest sugar cataract formation. Five topical suspensions of 3% 2-methylsorbinil (2-MS) were prepared using (1) hydroxypropyl methylcellulose (HPMC, 0.5% w/v), (2) xanthan gum (0.5% w/v), (3) gellan gum (0.5% w/v), (4) carbopol (0.25% w/v), and (5) carbopol (0.25% w/v)--hydroxypropyl methylcellulose (HPMC) (0.25% w/v). Lenticular levels of 2-MS was highest in rats administered suspensions containing 0.25% carbopol + 0.25% HPMC as vehicles followed by 0.5% gellan gum, 0.5% HPMC, 0.25% carbopol, and 0.5% xanthan gum.

Suri S et al\textsuperscript{22} evaluated biopolymers as in situ gels for short term vitreous substitution. Biophysical characterization revealed that the viscosity of the vitreous was >4000 cP at a shear rate of 0.15/s and it formed a gel with elastic modulus $G'$ greater than the viscous modulus $G''$. Biopolymers of gellan and hyaluronic acid (8:2 w/w, 1% concentration) were low viscosity liquids at 37°C and gelation was triggered both by the addition of 0.18 mM CaCl\textsubscript{2} as well as ocular temperature, thus making them feasible as in situ gels.

Sultana Y et al\textsuperscript{23} developed an ophthalmic delivery system of a fluoroquinolone antibiotic, pefloxacin mesylate, based on the concept of ion-activated in situ gelation. The formulations exhibited a first-order release pattern over 12 hr in \textit{in vitro} release studies. The developed formulation was effective against selected micro-organisms in antimicrobial efficacy studies.

Balasubramaniam J et al\textsuperscript{24} developed an ophthalmic delivery system of the NSAID indomethacin, based on the concept of ion activated in situ gelation. The developed formulations were therapeutically efficacious (in a uveitis induced rabbit eye model) and provided sustained release of the drug over an 8-hour period \textit{in vitro}.

Balasubramaniam J et al\textsuperscript{25} described the formulation and evaluation of an ophthalmic delivery system of an antibacterial agent, ciprofloxacin, based on the concept of ion-activated in situ gelation. Gelrite gellan gum, a novel ophthalmic vehicle that gels in the presence of mono or divalent cations, present in the lacrimal fluid was used alone and in combinations with sodium alginate as the gelling agent. The developed
formulations were therapeutically efficacious and provided sustained release of the drug over an 8-hr period in vitro.

Stewart WC et al\textsuperscript{26} evaluated the efficacy and safety of timolol maleate 0.5% gel forming solution (TXE, Merck) versus timolol maleate 0.5% gel forming solution (TXG, Falcon) in primary open-angle glaucoma and ocular hypertension patients. It was concluded from the study that TXE demonstrates a lower intraocular pressure eight hours after dosing than does TXG, but safety appeared similar between products.

Shedden A et al\textsuperscript{27} formulated timolol in a highly purified gellan gum to improve its duration of action. The efficacy of this formulation in short-term studies using once-daily dosing has been reported. The purpose of this study was to evaluate the efficacy and tolerability of 0.5% timolol maleate ophthalmic gel-forming solution (timolol GS) given once daily versus 0.5% timolol solution given twice daily in a long-term trial. It was concluded from the study that Timolol 0.5% GS administered once daily was shown to be as effective in lowering IOP as the equivalent concentration of timolol 0.5% solution administered twice daily in patients with ocular hypertension or open-angle glaucoma.

Hagerstrom H et al\textsuperscript{28} evaluated a rheological method to measure mucoadhesion for two ion-sensitive polymers, Carbopol 934 and Gelrite (deacetylated gellan gum), in a simulated physiological environment using two commercially available mucins.

Paulsson M et al\textsuperscript{29} studied the rheological behaviour of deacetylated gellan gum (Gelrite) was analysed in order to better understand the reasons for the good performance in humans. The findings explained the good performance of Gelrite in vivo. Gels with a high elastic modulus can thus be formed even though dilution of instilled drops takes place.

Dickstein et al\textsuperscript{30} compared, in healthy human volunteers (male and female), the corneal contact time of various formulations, and each containing one viscosity enhancer from the following list: a phase-transition system (gellan gum), a
heteropolysaccharide (xanthan gum) and currently used polymers hydroxyethylcellulose, hydroxypropylmethylcellulose, or polyvinyl alcohol. The results confirmed that an increase in viscosity of the formulation delays the clearance of the instilled solution by the tear flow. The effect of the gelation mechanism was superior, especially at the later time points. In this respect they concluded that xanthan gum and, particularly, Gelrite are suitable vehicles for ophthalmic drugs.

Laurence J et al\textsuperscript{31} evaluated a topical formulation of timolol in an anionic heteropolysaccharide gellan gum (Gelrite). Within each concentration at several observation points, the gel formulation elicited a 1-2-mm Hg greater efficacy than the solution. This study concluded that formulation of timolol with a gel may increase efficacy, and thus duration of action. This may possibly allow use of a lower concentration of timolol or a reduced frequency of instillation.

Gunning FP et al\textsuperscript{32} investigated the ocular hypotensive activities of the two potent topical carbonic anhydrase inhibitors sezolamide and dorzolamide were compared formulated in Gelrite vehicle, a novel ophthalmic drug delivery system. Duration of action of both compounds was, at most, slightly prolonged by the use of Gelrite vehicle when compared with former studies on sezolamide and dorzolamide.

Balasubramaniam J et al\textsuperscript{33} prepared film-type scleral implants of indomethacin with gellan gum by solvent casting and evaluated for uniformities of thickness, weight, drug content, and surface pH. The pharmacodynamic studies showed a marked improvement in the various clinical parameters (congestion, keratitis, flare, clot, aqueous cells, and synechias) in the implanted eye compared with the control eye in the rabbits. The scleral implants survived up to 3 weeks \textit{in vivo}.

Carlfors J et al\textsuperscript{34} studied the rheology of Gelrite in situ gels. The human contact times increased up to 20 h with decreasing osmolality of the formulations. The results indicated that a high rate of the sol/gel transition results in long contact times.

El-Laithy et al\textsuperscript{35} prepared and evaluated six in situ gelling formulations based on Gelrite for the retained ophthalmic delivery of Moxifloxacin (Mox). The effectiveness
of the best developed formula G5 was compared with photodynamic therapy (PDT), the recent expanding approach for the treatment of ophthalmologic disorders after the assessment of optimum photodynamic inactivation parameters that permit efficient pathogens eradication. After post corneal infection with S. aureus, both approaches were effectively treating the infection without causing ocular irritation or collateral damage to corneal tissue where G5 showed remarkable improvement after four days compared to seven days of PDT treatment.

El-Kamel et al\textsuperscript{36} developed environmentally responsive gel formulation for ocular controlled delivery of carteolol hydrochloride in an attempt to improve ocular bioavailability and hence decrease its systemic absorption and side effects. The viscosity and the ability of the prepared formulations to deliver carteolol HCl \textit{in vitro} and \textit{in vivo} were monitored and compared with an aqueous commercial solution. Gelrite formulations showed pseudoplastic behavior with thixotropic characteristics and the viscosity of the prepared systems increased as the concentration of the polymer increased. At fixed drug concentrations, as the Gelrite concentration increased, the drug release decreased. Gelrite formulation (0.4\% w/w) containing 1\% drug showed significantly improved bioavailability compared with the commercial aqueous solution.
3.3.2. Carbopol - 934P (Carbomer)

Deshmukh PK et al\textsuperscript{37} developed novel environmentally responsive ophthalmic drug delivery system composed of two gelling polymers with different phase transition mechanisms in order to obtain sustained drug release in ocular cavity. Combination of polyacrylie acid (carbopol 934P) and xanthan gum was investigated as ophthalmic vehicle and assessed for its \textit{in vitro} and \textit{in vivo} performance. On the basis of these findings, environmentally responsive system based on combination of carbopol and xanthan gum could be considered as a promising tool for ophthalmic delivery.

Aburahma MH et al\textsuperscript{38} enhanced ocular bioavailability of brimonidine, a potent antiglaucoma drug, through the preparation of ocular inserts. Solvent casting technique was employed to prepare the inserts using polyvinylpyrrolidone K-90 (PVP K-90) as film-forming polymer blended with different viscosity grades of bioadhesive polymers namely hydroxypropyl methylcellulose, carbopol, sodium alginate, and chitosan.

Kesavan K et al\textsuperscript{39} studied HP-\textbeta-CD based pH-induced mucoadhesive hydrogel for ophthalmic delivery of Dexamethasone (DXN) to treat uveitis. To improve ocular retention and sustained action Carbopol 980 NF and sodium carboxymethylcellulose (NaCMC) were added to the formulations as phase transition and mucoadhesive agents, respectively. The developed HP-\textbeta-CD-based mucoadhesive system was a viable alternative to conventional eye drops of DXN due to its ability to enhance bioavailability through its longer precorneal residence time and ability to sustain the release of the drug.

Asasutjarit R et al\textsuperscript{40} conducted study to optimize and evaluate Pluronic F127-based thermoresponsive diclofenac sodium ophthalmic in situ gels. In this study, Carbopol 940 did not affect sol-gel transition temperature but it affected transparency, pH, and gelling capacity of the products. The optimized formulation exhibited sol-gel transition at 32.6 ± 1.1 °C with pseudoplastic flow behavior.
Wu H et al\textsuperscript{41} investigated the correlation between the stability of baicalin and in situ pH-triggered gelling system. Carbopol(\textsuperscript{®}) 974P (0.3\%, w/v) was used as the gelling agent combined with hydroxypropylmethylcellulose E4M (0.6\%, w/v) which acted as a viscosity enhancing agent. The results demonstrated that an in situ pH-triggered gelling system have better ability to keep baicalin stable and retain drug release than marketed baicalin eye drops to enhance the ocular bioavailability.

Parikh R. et al\textsuperscript{42} described the formulation development of ophthalmic in situ gelling system using thermo-reversible gelling polymer, i.e. Pluronic F 127 (PF127). So, to reduce this concentration, an attempt was made to combine the PF127 with other polymers like hydroxy propyl methyl cellulose (HPMC) as a viscosity increasing agent or with polymers like carbopol 940, xanthan gum, and sodium alginate (high glucuronic acid content) showing a pH and cation-triggered sol-gel transition, respectively. It was concluded that using this type of combination system, it could reduce not only the concentration of individual polymers but also the side effects without compromising the \textit{in vitro} gelling capacity as well as overall rheology of the system.

Vyas SP et al\textsuperscript{43} described the formulation and evaluation of an ophthalmic delivery system of an antiglaucoma drug, timolol maleate (TM) based on the concept of pH-triggered in situ gelation. Polyacrylic acid (carbopol) was used as the gelling agent in combination with chitosan (amine polysaccharide), which was acted as a viscosity-enhancing agent. The results clearly demonstrated that developed carbopol-chitosan based formulation was therapeutically efficacious and showed a fickian (diffusion controlled) type of release behaviour over 24 h periods.

Cao F et al\textsuperscript{44} focused on preparation and evaluation of a thermosensitive and mucoadhesive in situ gelling ophthalmic system of azithromycin (ATM). Poloxamer 407 (P407) and poloxamer 188 (P188) were used as gelling agents. Addition of Carbopol 974P (CP 974P) to the gelling systems could increase the solubility of ATM by salt effect and enhance the mucoadhesive property of the systems.
Paliwal SK et al\textsuperscript{45} studied adhesive strength of various polymers on corneal surface with the help of self modified Franz diffusion cell and freshly excised goat/bovine cornea. The polymers hydroxypropylmethylcellulose, carboxymethylcellulose sodium, Eudragit type E/RL/RS, Carbopol ETD 2020 and Carbopol 934 with drug, ketorolac tromethamine. Observations made in this study indicated the potentiality of the ophthalmic formulations containing mucoadhesive/viscosity imparting agents.

Hosny KM\textsuperscript{46} prepared and characterized an ocular effective prolonged-release liposomal hydrogel formulation containing ciprofloxacin. For hydrogel preparation, Carbopol 940 was applied. In vitro transcorneal permeation through excised albino rabbit cornea was also determined. Optimal encapsulation efficiency of 73.04 +/- 3.06% was obtained from liposomes formulated with PC/CH at molar ratio of 5:3 and by increasing CH content above this limit, the encapsulation decreased. The results suggested that the degree of encapsulation of ciprofloxacin into liposomes and prolonged \textit{in vitro} release depend on composition of the vesicles. In addition, the polymer hydrogel used in preparation ensure steady and prolonged transcorneal permeation.

Afouna MI et al\textsuperscript{47} Dorzolamide hydrochloride (DZD) was formulated as 2% formulations ophthalmic gels containing different concentrations of C-934 as mucoadhesive, as well as, with various concentrations of terpene-4-ol as a natural corneal penetration enhancers.

Al-Kassas RS et al\textsuperscript{48} performed a study to design controlled release ophthalmic delivery systems for ciprofloxacin based on polymeric carriers that undergo sol-to-gel transition upon change in pH or in the presence of cations in an attempt to prolong the effect of ciprofloxacin and improve its ocular bioavailability. Carbopol and alginates polymers were used to confer gelation properties to the formulations. Hydroxypropyl methylcellulose and methylcellulose were combined with carbopol to increase the viscosity of the gels and to reduce the concentration of the incorporated carbopol. Controlled release in situ gels consisting of carbopol and cellulose derivatives showed an increase in viscosity, gelling capacity, and adhesiveness as the concentration of

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each polymeric component was increased. On the other hand, these parameters possessed lowest values when alginate was used as an in situ gelling agent.

Jain SP et al\textsuperscript{49} prepared and evaluated a once a day ophthalmic delivery system for ciprofloxacin hydrochloride based on the concept of pH-triggered in situ gelation. The in situ gelling system involved the use of polyacrylic acid (Carbopol 980NF) as a phase transition polymer, hydroxypropyl methylcellulose (Methocel K100LV) as a release retardant, and ion exchange resin as a complexing agent. The developed formulation was stable and nonirritant to rabbit eyes and \textit{in vitro} drug release was found to be around 98\% over a period of 24 hours.

Ma WD et al\textsuperscript{50} investigated rheological properties and \textit{in vitro} drug release of Pluronic-g-PAA copolymer gels, as well as the \textit{in vivo} resident properties of in situ gel ophthalmic formulations. The rheogram and \textit{in vitro} drug release studies indicated that the drug release rates decreased as acrylic acid/Pluronic molar ratio and copolymer solution concentration increased. In vivo resident experiments showed the drug resident time and the total resident amount increased by 4-fold and 1.2-fold for in situ gel compared with eye drops. These \textit{in vivo} experimental results, along with the rheological properties and \textit{in vitro} drug release studies, demonstrated that in situ gels containing Pluronic-g-PAA copolymer may significantly prolong the drug resident time and thus improve bioavailability.

Ma WD et al\textsuperscript{51} studied Pluronic F127-g-poly(acrylic acid) copolymers as in situ gelling vehicle for ophthalmic drug delivery system to prolong the precorneal resident time and improve ocular bioavailability of the drug. The decreased loss angle at body temperature and prolonged precorneal resident time also indicated that the copolymer gels had bioadhesive properties. These \textit{in vivo} experimental results, along with the rheological properties and \textit{in vitro} drug release studies, demonstrated that in situ gels containing Pluronic-g-PAA copolymer may significantly prolong the drug resident time and thus improve bioavailability.

Qi H et al\textsuperscript{52} developed 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.

Wu C et al.\textsuperscript{53} developed a pH-triggered in situ gelling vehicle for ophthalmic delivery of puerarin. Carbopol 980NF was used as the gelling agent in combination with HPMC (Methocel E4M) which acted as a viscosity-enhancing agent. Both \textit{in vitro} release studies and \textit{in vivo} pharmacokinetics studies indicated that the combined polymer systems performed better in retaining puerarin than puerarin eye drops did.

Sultana Y et al.\textsuperscript{54} developed and characterized a series of carbopol- and methyl cellulose-based solutions as the in situ gelling vehicles for ophthalmic drug delivery. The rheological properties, \textit{in vitro} release as well as \textit{in vivo} pharmacological response of a combination of polymer solutions, including carbopol and methyl cellulose, were evaluated. The results demonstrated that the carbopol/methyl cellulose mixture can be used as an in situ gelling vehicle to enhance the ocular bioavailability of pefloxacin mesylate.

Kaur IP et al.\textsuperscript{55} studied water soluble polymers that have been reported to improve the complexing capabilities of beta-cyclodextrins. In the present study water soluble polymers like polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), hydroxypropylmethylcellulose (HPMC) and the mucoadhesive polymer Carbopol 934P were incorporated into aqueous 10% w/v 2HP-beta-CD solution to improve the solubility of acetazolamide.

Homof et al.\textsuperscript{56} developed a mucoadhesive ocular insert for the controlled delivery of ophthalmic drugs and to evaluate its efficacy \textit{in vivo}. The inserts tested were based either on unmodified or thiolated poly(acrylic acid). Inserts based on thiolated poly(acrylic acid) were not soluble and had good cohesive properties. The \textit{in vivo} study showed that inserts based on thiolated poly (acrylic acid) provide a fluorescein
concentration on the eye surface for more than 8 h, whereas the fluorescein 
concentration rapidly decreased after application of aqueous eye drops. 
Aktaş Y et al\textsuperscript{57} investigated the influence of hydroxypropyl beta-cyclodextrin (HP-
beta-CD) on the corneal permeation of pilocarpine nitrate by an \textit{in vitro} permeability 
study using isolated rabbit cornea. The reduction of pupil diameter (miosis) by 
pilocarpine nitrate was significantly increased as a result of HP-beta-CD addition into 
the simple aqueous solution of the active substance. The highest miotic response was 
obtained with the formulation prepared in a vehicle of Carbopol 940.

Wei G et al\textsuperscript{58} evaluated how solution viscosity affects the precorneal residence of five 
water-soluble polymers with different properties. Carbopol and sodium hyaluronate 
(HA), which adsorbed to isolated ocular surface more than 15 min, showed the 
optimum precorneal retentive capabilities. When the solution viscosity increased from 
12 mPa.s to 50 mPa.s, the residence time of carbopol and HA was prolonged 10 min 
and 7 min, respectively, but that of sodium carboxymethylcellulose was not affected. 
It was concluded that the higher viscosity is beneficial to improve the ocular residence 
time of bio-adhesive polymers.

Charoo NA et al\textsuperscript{59} prepared Sol-to-gel systems of ciprofloxacin hydrochloride 
utilizing the phase transition properties of hydroxy propyl methyl cellulose K 15 M 
grade (HPMC) and carbopol 934. The sol-to-gel system exhibited a zero-order drug 
release pattern over 24 h \textit{in vitro} release studies. The drug was active against selected 
microorganisms in microbial efficacy studies. Better improvement in artificially 
induced bacterial conjunctivitis in rabbits' eyes was observed in animals treated with 
the sol-to-gel system compared with marketed eye drops. 
Ke TL et al\textsuperscript{60} prepared the formulation system consisted of a viscosity enhancer 
(carbopol gel or hydroxypropylmethylcellulose solution) plus a penetration enhancer 
(dodecylmaltoside) to overcome penetration barriers and loss due to wash-out and 
thus achieve the desired ciprofloxacin ocular absorption.
Srividya B et al\textsuperscript{61} described the formulation and evaluation of an ophthalmic delivery system of an antibacterial agent, ofloxacin, based on the concept of pH-triggered in situ gelation. Polyacrylic acid (Carbopol 940) was used as the gelling agent in combination with hydroxypropylmethylcellulose (Methocel E50LV) which acted as a viscosity enhancing agent.

Lin HR et al\textsuperscript{62} developed and characterized a series of carbopol- and pluronic-based solutions as the in situ gelling vehicles for ophthalmic drug delivery. Both the \textit{in vitro} release and \textit{in vivo} pharmacological studies indicated that the carbopol/pluronic solution had the better ability to retain drug than the carbopol or pluronic solutions alone.

Hagerstrom H et al\textsuperscript{28} studied rheological method to measure mucoadhesion was evaluated for two polymers Carbopol 934 and Gelrite((R)) (deacetylated gellan gum), in a simulated physiological environment using two commercially available mucins.

Wilson CG et al\textsuperscript{63} studied ocular contact time of carbomer gels conducted in humans. These studies demonstrated that carbomer based gels significantly extends contact of solutes or suspended solids with the corneal surface. The method of labelling did not significantly change the initial viscosity

Kumar S et al\textsuperscript{64} studied aqueous solutions of Carbopol [polyacrylic acid (PAA)] which are low viscosity acidic solutions that transform into gels upon an increase in the pH and, therefore, may be used as in situ gelling ophthalmic drug delivery systems. However, the amount of PAA required in the solution to form stiff gels upon installation in the eye is not easily neutralized by the buffering action of tear fluid. The rheological properties of aqueous solutions containing PAA and hydroxypropyl methylcellulose (HPMC), a viscosity-enhancing polymer, evaluated as a function of temperature and pH, were similar to those of pure PAA solutions; that is, both form
low viscosity liquids at pH 4.0 and transform into stiff gels with plastic rheological behavior and comparable viscosities upon increasing the pH to 7.4.

Kumar S et al\textsuperscript{65} studied, the rheological characterization of such a system, prepared by a combination of Carbopol (C) and methyl cellulose (MC), was carried out at two different pH (4.0 and 7.4) and temperatures (25 and 37 degrees C) by rotational cone and plate viscometry.

Unlu N et al\textsuperscript{66} investigated the rheological behaviours of different types of Carbopol (Carbopol 940, 934, 941 and 910) in this work. Viscous solutions of these polymers were prepared in the range of concentration between 0.01-0.25 percent (w/w). 10% aqueous solution of sodium hydroxide was used for the neutralization procedure. Mannitol, sorbitol, sodium chloride and borate were tested to make the isotonic solutions. The viscosities of the solutions decreased dramatically with sodium chloride and sodium borate. Mannitol had no effect on the pH values of the solutions while sorbitol has showed a small effect. It was concluded that four types of Carbopol are suitable for ophthalmic use.

Unlu N et al\textsuperscript{67} prepared Carbopol 940 ophthalmic vehicles in order to investigate the interaction between the simulated lacrimal fluid and the polymer, and to examine the influence of sodium fluorescein - a tracer for the fluorophotometric studies - on the physico-chemical properties of the polymer vehicles.

Davies NM et al\textsuperscript{68} Compared precorneal clearance of a mucoadhesive polymer solution (Carbopol 934P) to that of an equiviscous non-mucoadhesive poly(vinyl alcohol) solution (PVA) and buffer (PBS). Carbopol 934P solution produces a significant increase (P less than 0.05) in bioavailability as compared to PVA and PBS.

Weyenberg W et al\textsuperscript{69} employed different rheological characterisation methods to investigate the influence of the sterilisation method (autoclaving), the polymer concentration (0.50, 0.75 and 1.00%) and the dispersing medium (i.e. isotonic
phosphate buffer and mannitol solution) on Carbopol 974 P NF dispersions, used as ocular gels. The rheological data showed that the choice of the dispersing medium has a significant influence on the rheological behaviour of the ocular gels prepared.

Herrero-Vanrell R et al\textsuperscript{50} evaluated how the addition of mucoadhesive polymers to aqueous solutions affects the ocular response of tropicamide (0.2%; w/v). The polymer solutions tested were carboxymethylcellulose sodium salt (CMC-Na; 1%; w/v), hyaluronic acid sodium salt (HA-Na; 0.1%; w/v) and polyacrylic acid (PAA; 0.2%; w/v).

Deshpande SG et al\textsuperscript{71} prepared and evaluated Gels containing pilocarpine by measuring the intensity and duration of miotic response in albino rabbits. Carbopol-940 gels, being the best of those used, were studied further for the effect of its concentration and of additives (benzalkonium chloride, phenylmercuric nitrate, chlorbutol and disodium edetate), autoclaving at 121 degrees C for 30 min and irradiation with gamma rays (2.5 Mrad), on the end product.
3.3.3. Benzododecinium bromide

Bai T et al\textsuperscript{72} compared the short-term effects of preserved and unpreserved topical levofloxacin on the ocular surface of preoperative patients with age-related cataracts. Regarding the short-term effects on the ocular surface of patients with age-related cataracts, no clinically and statistically significant differences were observed between topical levofloxacin preserved with Benzododecinium bromide and its unpreserved counterpart.

Debbasch C et al\textsuperscript{73} investigated some of the toxicity mechanisms of 10 preservatives currently used in ophthalmic solutions \textit{in vitro}. An apoptotic mechanism appeared to be present at low concentrations of quaternary ammoniums, like Benzododecinium bromide whereas a necrotic process appeared at higher concentrations. Superoxide anions may play an important role in tissue damage induced by preservatives in ocular surface disorders.

Pisella PJ et al\textsuperscript{74} used rabbits to study their ocular tolerance to (a) 0.25 and 0.50\% Timoptol preserved with 0.01\% benzalkonium chloride, (b) 0.25 and 0.50\% Timoptol-LP, a gel-forming solution preserved with 0.012\% benzododecinium bromide, and (c) 0.25 and 0.50\% Timabak unpreserved in the ABAK eyedrops dispenser. This study confirms that using unpreserved timolol may be beneficial for the long-term treatment of glaucomatous patients as it increases tear film stability and decreases epithelial permeability and stromal aggression of the cornea.

Becquet F et al\textsuperscript{75} performed a comparative study to investigate toxic side effects induced in the rat ocular surface by applications of various preservatives, with special attention to inflammatory infiltrates. This study confirms that most preservatives used in ophthalmic eyedrops may similarly induce histopathological and inflammatory changes in the ocular surface after short term use.
Debbasch C et al\textsuperscript{76} evaluated \textit{in vitro} cytotoxicity of quaternary ammonium. This study observed \textit{in vitro} can explain some of the ocular surface damage caused by long-term use of preserved eye-drops.

### Table 3.1 Literature review about Patented Ocular drug delivery technology

<table>
<thead>
<tr>
<th>Example of Invention</th>
<th>Key Technology</th>
<th>Patent Application No. #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betaxolol hydrochloride and Levobetaxolol HCl/Glaucoma</td>
<td>Sustained drug release and improved comfort using ion-exchange resin/polyanionic polymer/pH adjusting agent</td>
<td>US6486208B1</td>
</tr>
<tr>
<td>Linezolid/Infection</td>
<td>Increased drug retention in eyes using gums (konjac, scleroglucan, propylene glycol alginate)</td>
<td>US20030232089A1</td>
</tr>
<tr>
<td>Roflumilast/Allergy and inflammation</td>
<td>Enhanced efficacy using viscosity-increasing agents</td>
<td>EP1889620A1</td>
</tr>
<tr>
<td>Beta blockers/Glaucoma</td>
<td>Formulated ophthalmic gels using carbopol to enhance IOP reduction</td>
<td>WO0035439</td>
</tr>
<tr>
<td>Betaxolol HCl/Glaucoma</td>
<td>Delayed drug release using cross-linked poly(styrenedivinyl) benzene cation exchange resin</td>
<td>US6258350 B1</td>
</tr>
<tr>
<td>NSAIDs/Inflammation and pain</td>
<td>Sustained drug release from micelle solutions containing designed block copolymers</td>
<td>US20020064513A1</td>
</tr>
<tr>
<td>Olopatadine/Allergy</td>
<td>Preserved formulations using a gentle preservative, such as SCD</td>
<td>US20050209312A1</td>
</tr>
<tr>
<td>Hyaluronic acid/Dry eye</td>
<td>Improved viscosity and efficacy of ophthalmic formulations using a combination of hyaluronic acid and polyvinyl alcohol for the treatment of dry eye</td>
<td>US20080050335A1</td>
</tr>
</tbody>
</table>
3.4. Review of work done on Periodontal drug delivery system utilizing

3.4.1. Poloxamer-407 and/or Chitosan

H.M. Kelly et al\textsuperscript{77} developed a novel drug delivery system for the treatment of periodontitis using two components. The first was tetracycline base loaded into the microtubular excipient halloysite, which was coated with chitosan to further retard drug release. A final formulation was developed which consisted of 200 mg of halloysite double loaded with tetracycline base and coated with chitosan, suspended in 1 ml of poloxamer 407 20% (w/w), PEG 20,000 0.5% (w/w), OCA 1.0% (w/w), water to 100%, adjusted to pH 4. The syringeability of this formulation at various temperatures was evaluated to ensure ease of delivery to the periodontal pocket. This formulation offered ease of delivery to the periodontal pocket and sustained release of the antibiotic for up to 6 weeks. The formulation had preliminary \textit{in vivo} testing performed in dogs to determine levels of drug release, antimicrobial activity and retentive ability of the product.

D.S. Jones et al\textsuperscript{78} described the formulation and characterisation of the viscoelastic, mechanical and mucoadhesive properties of thermoresponsive, binary polymeric systems composed of poloxamer (P407) and poly(acrylic acid, C974P) that were designed for use as a drug delivery platform within the oral cavity. The ease of administration (below the T\text{sol}/gel) in conjunction with the viscoelastic (notably high elasticity) and mucoadhesive properties (at body temperature) render the formulations composed of 20% (w/w) P407 and C934P as potentially useful platforms for mucoadhesive, controlled topical drug delivery within the oral cavity.

N. Bhattarai et al\textsuperscript{79} investigated the newest developments in chitosan hydrogel preparation and defined the design parameters in the development of physically and chemically cross-linked hydrogels. The advanced development of chitosan hydrogels has led to new drug delivery systems that release their payloads under varying conditions.
environmental stimuli. In addition, thermosensitive hydrogel variants have been developed to form a chitosan hydrogel in situ, precluding the need for surgical implantation.

S. Shanmuganathan et al\textsuperscript{80} developed Doxycycline-loaded chitosan microspheres using a novel water-in-oil emulsion technique, involving oil phase ionic gelation. Microspheres were prepared by using 6\% v/v of chitosan (3\% w/v in acetic acid), soya oil–n-octanol oil mixture (1:2 v/v) as continuous phase and 5\% span 80 as emulsifier. Doxycycline was entrapped by equilibrium swelling method with 8.4\% total entrapment.

T. Ur-Rehman et al\textsuperscript{81} developed a method for the in situ gelation of poloxamers and the mucoadhesive polymer chitosan by exploiting the tendency of poloxamer solution to form gel at physiological temperatures and of chitosan to form ionotropic gel structures in the presence of sodium tripolyphosphate (TPP). These in situ gels had the potential to increase the utility of thermo-reversible poloxamers in drug delivery.

S. Govender et al\textsuperscript{82} employed a Box-Behnken experimental design to statistically optimise the formulation parameters of a tetracycline microsphere preparation for maximum bioadhesivity and controlled drug release.

L. Perioli et al\textsuperscript{83} prepared mucoadhesive tablets using different mixture of cellulose and polyacrylic derivatives in order to obtain new formulations containing metronidazole for periodontal disease treatment. The chosen tablet, containing 20 mg of metronidazole, performed 12 h drug sustained release with buccal concentrations always higher than its MIC.

R. Elkayam et al\textsuperscript{84} developed a system for the sustained release of minocycline for use in the treatment of periodontal diseases. The release rate and the antibacterial activity of minocycline were measured \textit{in vitro} and \textit{in vivo}. The results of the short-term clinical study indicate that use of the device in periodontal pockets may cause complete eradication of the pathogenic bacteria from the pocket.
R.C. Mundargi et al. developed a novel biodegradable microspheres prepared by water-in-oil-water (W/O/W) double emulsion technique using the blends of poly(D,L-lactide-co-glycolide) (PLGA) and poly(ε-caprolactone) (PCL) in different ratios for the controlled delivery of doxycycline. Doxycycline encapsulation of up to 24% was achieved within the polymeric microspheres. One of the developed formulations was subjected to in vivo efficacy studies in thirty sites of human periodontal pockets. Significant results were obtained with respect to both microbiological and clinical parameters up to 3 months even as compared to commercial doxycycline gel.

L.E. Bromberg et al. described a conceptually novel periodontal drug delivery system intended for treatment of microbial infections associated with periodontitis. In vitro experiments demonstrated that the wafers are capable of zero-order release of antimicrobial agents such as silver nitrate, benzylpenicillin, and tetracycline, for over 4 weeks.

Marcos L. Bruschi et al. designed formulations containing poloxamer 407, carbopol 934P (C934P), and propolis extract (PE) for the treatment of periodontal disease. The work of syringeability values of all formulations were similar and very desirable with regard to ease of administration. The data obtained in these formulations indicated a potentially useful role in the treatment of periodontitis and suggested they are worthy of clinical evaluation.

M.L. Veyries et al. investigated Poloxamer 407 25% (w/w) formulations aimed at prolonging the residence time of vancomycin, a time-dependent antibiotic, in a body site with a high infectious risk. Controlled-release profiles, good preservation of vancomycin activity, good tolerability in rats, and ease of administration suggested that Poloxamer 407 may be useful as a vancomycin delivery vehicle for local prophylaxis of infections, especially in prosthetic surgery.

E. Esposito et al. developed tetracycline-containing formulations for the treatment of periodontitis by direct periodontal intrapocket administration. Two different semi-
solid formulations were prepared, based on poly(oxyethylene)poly(oxypropylene) block copolymer (poloxamer) and monoglycerides, respectively. Both formulations possess interesting properties as delivery systems. These latest studies indicated that both poloxamer and monoglycerides gels, when applied subgingivally, produce a significantly improved outcome in moderate to deep periodontal pockets.

Akncbay H et al\textsuperscript{90} evaluated the clinical effectiveness of chitosan, both as a carrier in gel form and as an active agent in the treatment of chronic periodontitis. It was suggested that chitosan itself is effective as well as its combination with metronidazole in CP treatment due to its antimicrobial properties.

Parikh R et al\textsuperscript{91} designed Smart gel periodontal drug delivery systems (SGPDDS) containing gellan gum, lutrol F127, and ornidazole (1\% w/v) for the treatment of periodontal diseases. In conclusion, the formulations described offer a wide range of physical and drug release characteristics.

Maze GI et al\textsuperscript{92} assessed tetracycline release and safety following a single application of a syringable 35\% tetracycline hydrochloride in a lactic-glycolic acid gel. Based upon the reduction in probing depths and \% of sites bleeding on probing at 8 days relative to pretreatment, and the absence of any serious adverse events, it was concluded that these bioerodible gels are safe, and since the bacteriostatic range for most putative periodontopathogens is in the 2-10 micrograms/ml range, the tetracycline levels observed at days 3 and 8 likely.
3.4.2. Polyethylene Glycol

Yuan Y et al\(^9\) developed thermosensitive and mucoadhesive rectal in situ gel of nimesulide by using mucoadhesive polymers such as sodium alginate and HPMC. These gels were prepared by addition of mucoadhesive polymers (0.5\%) to the formulations of thermosensitive gelling solution containing poloxamer 407 (18\%) and nimesulide (2.0\%). Polyethylene glycol (PEG) was used to modify gelation temperature and drug release properties.

Oliveira CP et al\(^9\) studied that the solubilisation of griseofulvin in 1\% aqueous micellar solutions of Pluronic F127 at 37\( ^\circ \text{C} \) has been modified by adding polyethylene glycol PEG 35000 or poly(vinylpyrrolidone) PVP K30. The solubilisation capacity expressed in terms of unit weight of F127 is increased by the addition of 0.5wt\% PEG 35000 to a value approaching double that of a 2.5wt\% solution of F127 alone, but there is no advantage in adding 0.5wt\% PVP K30.

Zaki NM et al\(^9\) developed a mucoadhesive in situ gel with reduced nasal mucociliary clearance in order to improve the bioavailability of the antiemetic drug, metoclopramide hydrochloride. The in situ gelation upon contact with nasal mucosa was conferred via the use of the thermogelling poloxamer 407 whereas mucoadhesion and drug release enhancement were modulated via the use of mucoadhesive and polyethylene glycol (PEG) polymers respectively. The study point to the potential of mucoadhesive nasal in situ gel in terms of ease of administration, accuracy of dosing, prolonged nasal residence and improved drug bioavailability.

Ricci EJ\(^9\) studied that alteration of P407 gel content can affect drug release rates. The inorganic salts and PEG 400 commonly included in the formulation of P407 gels can also change the rate at which a drug is released.

Pandit NK\(^9\) studied the formation and melting of poloxamer-407 gels in the presence of polyethylene glycols (PEGs) has been studied.
Ricci EJ et al.\textsuperscript{98} characterized thermal gelation of Poloxamer 407 lidocaine hydrochloride gels by rheological studies. In the present work, aqueous gels with lidocaine containing different concentrations of Poloxamer 407 and additives like inorganic salts NaCl, NaH\textsubscript{2}PO\textsubscript{4}, Na\textsubscript{2}CO\textsubscript{3} and PEG 400 were obtained.

Following is a list of novel patented periodontal drug delivery approaches available in market. But very few of them are available in India.

\textbf{Table 3.2 Novel periodontal drug delivery approaches available in market}

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Manufacturer</th>
<th>Drug</th>
<th>Type of system</th>
<th>Polymers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perio Chip</td>
<td>Perio Products, Jerusalem, Israel</td>
<td>Chlorhexidine</td>
<td>Film</td>
<td>Hydrolyzed gelatin (cross-linked with Glutaraldehyde)</td>
</tr>
<tr>
<td>Actisite</td>
<td>Alza Corp., Palo Alto, CA, USA</td>
<td>Tetracycline</td>
<td>Fiber</td>
<td></td>
</tr>
<tr>
<td>Elyzol</td>
<td>Dumex, Copenhagen, Denmark/Colgate palmolive</td>
<td>Metronidazole</td>
<td>Injectable Gel</td>
<td></td>
</tr>
<tr>
<td>Dentomycin</td>
<td>Lederle Div., Wayne, NJ, USA</td>
<td>Minocycline</td>
<td>Ointment</td>
<td></td>
</tr>
<tr>
<td>Atridox</td>
<td>Block Drug Corporation</td>
<td>Doxycycline</td>
<td>Injectable Gel</td>
<td>Poly (DL-lactide)</td>
</tr>
<tr>
<td>Arestin</td>
<td>Orapharma</td>
<td>Minocycline</td>
<td>Microspheres</td>
<td>Poly (glycolide-co dl-lactide)</td>
</tr>
<tr>
<td>Bonjela</td>
<td>Reckitt &amp; Colman Ltd</td>
<td>Choline Salicylate</td>
<td>Gel, Dental</td>
<td></td>
</tr>
<tr>
<td>Corsodyl gel</td>
<td>GlaxoSmithKline</td>
<td>Chlorhexidine Gluconate</td>
<td>Gel; Dental</td>
<td>Hydroxypropyl methyl cellulose (HPMC)</td>
</tr>
<tr>
<td>Oraqix</td>
<td>Dentsply Pharm</td>
<td>Lidocaine; Prilocaine</td>
<td>Gel; periodontal</td>
<td>Poloxamer 188 and Poloxamer 407</td>
</tr>
</tbody>
</table>
The exhaustive literature has revealed few important points which made us understand and investigate our research work systematically. We have analyzed critically a segment of a published body of knowledge through summary, classification, and comparison of prior research studies, reviews of literature, and theoretical articles to solve the problems associated with ocular and periodontal drug delivery through concept of in situ gelling systems. It helped us to build a solid background for selection of drugs and excipients to be used for formulating in situ gelling system. We came to know that there has been no study till reported for formulating ocular in situ gel of Olopatadine HCl using combination approach. We could also not found any information about corneal permeability enhancement effect of Benzododecinium bromide. We also found a very few work being done on syringeable, mucoadhesive in situ gelling system of doxycycline hyclate. There has been no any systemic study being reported on in situ gelling systems by application of experimental design.
3. Literature Review

3.5. References

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3. Literature Review


