TIMOLOL MALEATE A GOLD STANDARD DRUG IN GLAUCOMA USED AS OCULAR FILMS AND INSERTS: AN OVERVIEW

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ABSTRACT

The majority of eye diseases are treated with topical eye drops. The meagre bioavailability and beneficial answer exhibited by these conventional eye drops due to fast precorneal elimination of the drug may be surmount by the use of *in situ* gelling systems that are instilled as drops into the eye and undergo a sol-to-gel transition in the *cul-de-sac*. In recent years, increased attention has been given to the development of new systems for the delivery of ocular medication. A number of ocular delivery systems lengthen the extent of drug action by enhancement of corneal absorption; these include suspension, soluble gels and emulsions, hydrophilic ocular inserts, ion-pair associations, liposomes, niosomes, nanosuspension, nanoparticles and prodrugs. Other delivery systems endow with a controlled release of drugs, thus avoiding the pulse-entry with which side-effects are associated. These systems can be based on any of several different mechanisms, and include both erodible and nonerodible matrices, wafers. Timolol maleate was the first β-blocker to be used as an anti-glaucoma agent and to date remains as the standard because none of the newer beta blockers were found to be more effective. Timolol maleate has the longest record of safety and efficacy to lower IOP and is administered via eye drops one or more times per day. The critical step is to develop a formulation for timolol maleate that leads to sustained delivery for long time.

Keywords: Timolol maleate; erodible systems; ocular inserts; osmotic systems; ocular films

INTRODUCTION

Glaucoma is a progressive optic neuropathy with characteristic optic nerve head changes and decreases in retinal sensitivity that lead to visual loss. It has been said that there are about 14 million glaucoma patients in India, 67 million people worldwide and the disease ranks second as the basis for adventitious blindness[1-3]. To treat glaucoma, daily use of ophthalmic solutions plays an important role. Once the disease is diagnosed, treatment is required to stop progressive damage and generally medical treatment is the first therapeutic approach[4]. β- Adrenergic antagonists like Timolol maleate have been considered for many years as the drugs of choice in most cases, while other agents like adrenergic agonists and parasympatheticomimetic agents were used as second line drugs. However, new drugs have been introduced for glaucoma treatment, like selective α- agonists (Brimonidine tartrate), carbonic anhydrase inhibitors CAI's (acetazolamide, dorzolamide) and prostaglandins broadening the therapeutic choices[5-6].

Pilocarpine preparations have been used since the 1870s, but they require to administer them frequently everyday has been unfavourable for many patients. In the 1980s, beta-blockers were developed, reducing the administration frequency to twice a day. In 1999, prostaglandin-type ophthalmic preparations that require once-a-day administration appeared on the market, easing the burden of frequent administration. During the process of the development of these new ophthalmic agents, Ocusert®, a sustained-release pilocarpine preparation that is inserted intra-ocularly only once a week, was designed and applied clinically[7].

1. Progress in the Review of Literature

1.1 Drugs review[8-12]

Timolol maleate

1. **Name:** 2-Propanol, 1- (1, 1-dimethylethyl) amino-3-[[4-(4-morpholinyl)-1, 2, 5-thiadiazol-3-yl] oxy]-, (S)-, (Z)-2-butenedioate (1:1) (salt).

2. **Physico-chemical properties**

   Origin of the substance: timolol maleate has been prepared through a series of synthetic steps beginning with D-mannitol and acetone. It belongs to the class of thiadiazole class of compounds.

   Formulae:

   a.) Structural formula

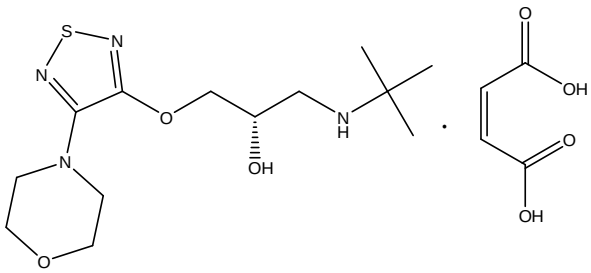

Figure 1: Structure of timolol maleate

b.) Molecular formula: $C_{13}H_{24}N_4O_3S.\ C_4H_4O_4$

c.) Molecular weight: 432.49

d.) pKa: 9.21

3. physical properties

a.) Appearance, color and odor: Timolol maleate is a white, odorless, crystalline powder.

b.) Melting point:202±0.5°C

c.) **Solubility:** The solubility of timolol maleate in a variety of solvents at room temperature (≈25°C) is presented in Table 1. Note that these solubilities are stated in terms of the current USP definitions.

Table 1: Solubility of timolol maleate in various solvents at room temperature

Solvent	Solubility
water	Soluble
Methanol	Soluble
Ethanol	Soluble
Chloroform	Sparingly Soluble
Propylene glycol	Sparingly Soluble
Ether	Practically insoluble
Cyclohexane	Practically insoluble
Isooctane	Practically insoluble

Packaging and storage: Preserve in well-closed containers.

4. Pharmacologic properties:

Category: Timolol maleate is a beta adrenergic blocker which is non-selective between beta-1 and beta-2 (β-1 and β-2) adrenergic receptors. It does not have significant intrinsic sympathomimetic, direct myocardial depressant or local anesthetic (membrane-stabilizing) activity. Timolol maleate is effective in lowering intraocular pressure (IOP) and is used in patients with open-angle glaucoma and aphakic glaucoma.

Timolol maleate is also indicated both for the treatment of hypertension (alone or combination with other thiazide-type diuretics) and to reduce cardiovascular mortality and the risk of reinfarction in patients who have survived the acute phase of myocardial infarction and who are clinically stable. Timolol maleate, available for oral dosing and tablets and for injection and ophthalmic dosing as distinct sterile aqueous solutions, is usually well tolerated with most adverse effects being mild and transient.

Mechanism of action: Blocks both β-1 and β-2 adrenergic receptors, reduces intraocular pressure by reducing aqueous humor production or possibly outflow; reduces blood pressure by blocking adrenergic receptors and decreasing sympathetic outflow, produces a negative chronotropic and inotropic activity through an unknown mechanism

5. Biopharmaceutics and metabolism

a.) Absorption and Bioavailability: Timolol maleate is rapidly and completely absorbed after oral administration. Maximum blood plasma concentrations ranging from 10ng/mL to 100 ng/mL are attained within 1 to 2.4 hours after either acute or chronic administration of 2.5 mg to 20 mg of timolol maleate twice daily. The bioavailability of oral timolol maleate is reported to be 61% to 75% of a reference intravenous dose. Bioavailability of less than 100% is attributed to first pass metabolic extraction by the liver after oral administration rather than to incomplete gastrointestinal absorption. The effect of food on the rate and extent of oral absorption of timolol maleate is not significant.

Pharmacodynamics/Kinetics

- Onset of action:
- Hypotensive: Oral: 15-45 minutes
- Peak effect: 0.5-2.5 hours
- Intraocular pressure reduction: Ophthalmic: 30 minutes
- Peak effect: 1-2 hours
- Duration: ~4 hours; Ophthalmic: Intraocular: 24 hours
- Protein binding: ~10%
- Metabolism: Extensively hepatic (80%) via cytochrome P450 2D6 isoenzyme; extensive first-pass effect
- Half-life elimination: 2.5-5 hours; prolonged with renal impairment
- Excretion: Urine (15% to 20% as unchanged drug)
- Toxicity: LD_{50}= 1190 mg/kg (oral, mice), LD_{50}= 900 mg/kg (oral, rat)

7. Contraindications

Hypersensitivity to timolol or any component of the formulation; sinus bradycardia; sinus node dysfunction; heart block greater than first degree (except in patients with a functioning artificial pacemaker); cardiogenic shock; uncompensated cardiac failure; bronchospastic disease; pregnancy (2nd and 3rd trimesters).

8. **Adverse Reactions**

- Ocular: Burning, stinging, blurred vision, cataract, conjunctival injection, itching, visual acuity decreased
- Cardiovascular: Hypertension
- Central nervous system: Headache
- Infection
- Cardiovascular: Bradycardia
- Central nervous system: Fatigue, dizziness, nausea and vomiting (Wolfhagen, F.S.H. *et al.*, 1998)
- Respiratory: Dyspnea

Over dosage/Toxicology

Symptoms of intoxication include cardiac disturbances, CNS toxicity, bronchospasm, hypoglycemia and hyperkalemia. The most common cardiac symptoms include hypotension and bradycardia. Atrioventricular block, intraventricular conduction disturbances, cardiogenic shock, and asystole may occur with severe overdose, especially with membrane-depressant drugs (e.g., propranolol). CNS effects including convulsions, coma, and respiratory arrest are commonly seen with propranolol and other membrane-depressant and lipid-soluble drugs. Treatment is symptom-directed and supportive.

Drug Interactions

- Albuterol (and other beta2 agonists): Effects may be blunted by nonspecific beta-blockers.
- Alpha-blockers (prazosin, terazosin): Concurrent use of beta-blockers may increase risk of orthostasis.
- AV conduction-slowing agents (digoxin): Effects may be additive with beta-blockers.
- Clonidine: Hypertensive crisis after or during withdrawal of either agent (not reported with timolol ophthalmic solution)
- CYP2D6 inhibitors: May increase the levels/effects of timolol. Example inhibitors include chlorpromazine, delavirdine, fluoxetine, miconazole, paroxetine, pergolide, quinidine, quinine, ritonavir, and ropinirole.
- Epinephrine (including local anesthetics with epinephrine): Timolol may cause hypertension.
- Glucagon: Timolol may blunt hyperglycemic action.
- Insulin and oral hypoglycemics: May mask symptoms of hypoglycemia.
- NSAIDs (ibuprofen, indomethacin, naproxen, piroxicam) may reduce the antihypertensive effects of beta-blockers.
- Salicylates may reduce the antihypertensive effects of beta-blockers.
- Sulfonylureas: Beta-blockers may alter response to hypoglycemic agents.
- Verapamil or diltiazem may have synergistic or additive pharmacological effects when taken concurrently with beta-blockers.

Stability

Ophthalmic drops: Store at room temperature; protect from light and freezing; Store in the protective foil wrap and use within 1 month after opening foil package.

Dosage

Ophthalmic: Children and Adults:

- Solution: Initial: Instill 1 drop (0.25% solution) twice daily; increase to 0.5% solution if response not adequate; decrease to 1 drop/day if controlled; do not exceed 1 drop twice daily of 0.5% solution.
- Gel-forming solution: Instill 1 drop (either 0.25% or 0.5% solution) once daily.
- Adults: Solution: Instill 1 drop (0.5% solution) once daily in the morning.

Oral: Adults:

- Hypertension: Initial: 10 mg twice daily, increase gradually every 7 days, usual dosage: 20-40 mg/day in 2 divided doses; maximum: 60 mg/day
- Prevention of myocardial infarction: 10 mg twice daily initiated within 1-4 weeks after infarction
- Migraine headache: Initial: 10 mg twice daily, increase to maximum of 30 mg/day

Ocular films reviews

Ocular films are sterile preparations with a solid or a semisolid consistency, and whose shape and size are designed for ocular application. They are composed of polymeric support containing or not drugs, the latter being incorporated as dispersion or a solution in the polymeric support.

In the recent years, there has been explosion of interest in the polymer based delivery devices, adding further dimension to topicals there by in the use of polymer such as collagen and fibrin fabricated into erodible inserts for placement in *cul-de-sac*. Utilization of the principles of controlled release as embodied by ocular inserts offers an attractive approach to the problem of prolonging precorneal drug residence times. Ocular inserts also offer the potential advantage of improving patient compliance by reducing the dosing frequency[13].

They may be for topical or systemic therapy with the main objective in addition to increasing the contact time being to ensure a sustained release suited for topical or systemic treatment. These solid ophthalmic devices present the following advantages[14-16]:

- Administration of an accurate dose in the eye and thus a better therapy.
- Comfort.
- Ease of handling and insertion.
- Ease of manufacture.
- Increased contact time and thus improved bio-availability.
- Lack of explosion.
- Non-interference with vision and oxygen permeability.
- Possibility of providing a prolonged drug release and thus a better efficacy.
- Reduction of systemic side effects and thus reduced adverse effects.
- Reduction of the number of administrations and thus better patient compliance.
- Reproductibility of release kinetics.
- Stability and finally.
- Sterility.

Recent work done on various ocular drug delivery systems

Rathore, K. S. *et al.*, (2010), formulated various formulations of films of brimonidine tartrate were using different polymers such as hypromellose and polyvinyl alcohol. Ocular films were characterized for thickness, surface pH, weight per square cm, percentage moisture absorption, percentage moisture loss, percent elongation, percentage drug released and in vitro residence time were performed by studying the diffusion through artificial membrane. After sterilization IR spectral studies were done to confirm the intactness of drug. In vitro study shows that delivery system is capable of releasing the drug in concentration independent mode, indeed the adaptability of delivery to biological membrane. In

conclusion, the ocular films formulation achieved the target of the above study such as reducing the frequency of administration, avoiding the drug loss due to lachrymal drainage and hence may increase patient compliance[17].

Jain, S.P. *et al.*, (2007), formulated and evaluated twice a day ocular inserts of acyclovir by melt extrusion method used for treatment of various ocular infections to improve patient compliance, using HPC as a thermoplastic polymer.the developed formulation overcome greasy nature of eye ointment, stable, non-irritant and provided release of the drug over a period of 10 hrs *in vitro*[18].

Abhilash, A.S. *et al.*, (2005), formulated ocular inserts of timolol maleate using different polymers at various concentrations. The polymers used were HPMC, EC, Eudragit RL 100 and RS 100. The ocuserts were evaluated for moisture absorption studies, moisture loss studies, thickness, weight uniformity, folding endurance, drug content, *in vitro* drug release studies and *in vivo* release studies[19].

Horwath-Winter *et al.*, (2005) treated human subjects suffering from dry eye syndrome with an antioxidant, iodide, using iontophoresis and demonstrated it to be a safe and well tolerated method of improving subjective and objective dry eye factors in patients with ocular surface disease[20].

Eljarrat-Binstock *et al.*, (2004) prepared solid hydrogels of hydroxyethyl methacrylate hydrogels (HEMA), cross-linked with ethylene glycol dimethacrylate, (EGDMA), and cross-linked arabinogalactan or dextrin to deliver gentamicin sulphate transscleraly. Transscleral iontophoretic treatment resulted in high concentrations of drugs in the posterior segments of the eye[21].

Hayden *et al.*, (2004) examined pharmacological logical distribution of carboplatin in New Zealand rabbits after its iontophoretic focal application (5.0 mA/cm^2, 20 minutes). They found iontophoretc delivery of carboplatin did not produce any toxicity in eye over sub-conjunctival injection[22].

Dandagi, P.M. *et al.*, (2004), developed Ocular films of cromolyn sodium by solvent casting technique using PVA and sodium alginate with glycerin and PEG 400 as plasticizers. The prepared films were evaluated for thickness, percent elongation at break, tensile strength and drug content uniformity, *in vitro* release studies and *in vivo* release studies[23].

Rao, V. and Shyale, S. (2004), formulated several ocular patches/inserts of norfloxacin-β-cyclodextrin in HPMC matrix. They studied the influence of rate controlling membranes made of ethyl cellulose (EC) alone and in combination with PVP K30 in different proportions on drug release kinetics. The films were evaluated for various physical characteristics. In vitro release studies were carried out in a fabricated flow through cell[24].

Charoo, N.A. *et al.*, (2003), developed reservoir type ocular inserts using sodium alginate containing ciprofloxacin hydrochloride as the core that was sandwiched between the Eudragit and/or polyvinyl acetate films. Ocular inserts were evaluated for *in vitro* release rate studies, microbial efficacy, *in vivo* release studies, efficacy against induced bacterial conjunctivitis in rabbit's eyes and stability studies[25].

Pandit, J.K. *et al.*, (2003), formulated polymeric ophthalmic inserts containing indomethacin with combinations of two different types of PVA (high-1, 25,000 and low-14,000 molecular weights) and physically reinforced by heating (80°C and 100°C for 24 and 48h) and freeze-thawing (3 and 6 cycles). They studied *in vitro* drug release permeation kinetics across goat cornea in a continuous flow-through apparatus and a modified Keshary-Chien cell, respectively, and compared with the non-reinforced inserts[26].

Vaithiyalingam, S. *et al.*, (2002), prepared aqueous based pseudolatex system of cellulose acetate butyrate (CAB) for controlled drug delivery. The pseudolatex films were prepared with CAB and PVA (stabilizer) by a polymer emulsification technique. The glass transition temperature, microscopic free volume, permeation coefficient, and mechanical properties of plasticized films were estimated. The films obtained were strong and flexible for controlled drug delivery applications[27].

Di Colo, G. and Zambito, Y. (2002), carried out studies on release mechanisms of different ophthalmic drugs from erodible ocular inserts based on poly (ethylene oxide). The respective contributions of diffusion and erosion to release mechanism of different drugs, namely, prednisolone, oxytetracycline hydrochloride and gentamicin sulfate from erodible ocular inserts based poly ethylene oxide of molecular weight 400 or 900kDa was determined by an *in vitro* technique adequate to predict the release mechanism *in vivo*[28].

Verma, P.R.P. *et al.*, (2001), fabricated cellulose acetate films by dissolving it in acetone. Dibutyl phthalate was used as a plasticizer. They casted films on mercury surface. The films were evaluated for relevant parameters[29].

Vijaya, C. *et al.*, (2001), prepared Chloramphenicol ocuserts using polymers such as HPMC, EC and Eudragit RL 100 at various concentrations. The drug reservoir was prepared with HPMC and rate controlling membrane was prepared with EC and Eudragit RL 100. The *in vitro* release studies were carried out using commercial semi permeable membrane. The physicochemical parameters of ocuserts were evaluated[30].

Jayaprakash, S. *et al.*, (2000), fabricated ocular inserts of ketorolac tromethamine using polymers such as HPMC, PVP, MC and EC at various concentrations. The *in vitro* release of the drug from the formulations was studied using commercial semi permeable membrane. The physicochemical parameters of inserts were evaluated[31].

Y.C., Lee *et al.*, (1999), formulated and evaluated a Gelfoam® (absorbable gelatin sponge, USP, size 100) based ocular device containing 1.7 mg phenylephrine and 0.6 mg tropicamide for papillary dilation in rabbits. The *in vivo* results show that the mydriatic response produced by the proposed device is larger and longer lasting than that produced by eyedrops with an equivalent amount of drugs[32].

Bharath, S. and Hiremath, S.R. (1999), prepared ocular films of pefloxacin mesylate using polymers such as HPC, HPMC, PVP and PVA in different ratios. The prepared films were evaluated for drug content, flexibility, *in vitro* release study and *in vivo* studies[33].

Saishivam, S. *et al.*, (1999), formulated ocusert of Ciprofloxacin Hydrochloride using different polymers in various proportions and combinations. The *in vitro* release of the drug from the formulations was studied using a commercial semi permeable membrane. The ocuserts were evaluated for various physico-chemical parameters[34].

Manikandar, R.V.M. *et al.*, (1998), formulated ophthalmic inserts of diclofenac sodium by using different polymers in various proportions. The *in vitro* release of the drug from the formulation was studied using a commercial ophthalmic membrane. The ophthalmic inserts were evaluated for various physico-chemical parameters[35].

Donnenfeld, E.D. *et al.*, (1997), investigated the intra-corneal, aqueous and vitreous penetration of Ofloxacin from the eye drop on administration to patients undergoing penetration keratoplasty with vitrectomy. They concluded that topically applied Ofloxacin achieves therapeutic levels in the cornea and aqueous humor. Mean levels achievable are well above the 90% minimal inhibitory concentration for the majority of bacteria responsible for endoophthalmitis and corneal ulceration[36].

Akkan, A.G. *et al.*, (1997), compared the aqueous humor penetration of topical 0.3% ciprofloxacin, 0.3% norfloxacin and 0.3% ofloxacin in 63 patients undergoing cataract surgery. They observed that topical ofloxacin achieved a significantly higher mean aqueous humor level than ciprofloxacin. All levels were above the minimum inhibitory concentrations for ciprofloxacin, ofloxacin and norfloxacin for most of the sensitive organisms[37].

Soppimath, K.S. *et al.*, (1997), prepared circular ophthalmic inserts of timolol maleate by solvent casting technique using cellulose acetate as polymer with PEG 600 and Diethyl phthalate as plasticizers in two different concentrations. They designed a new method for *in vitro* release study[38].

Narasimha Murthy, S. (1997), described the preparation and *in vitro- in vivo* evaluation of polymeric ophthalmic inserts containing diclofenac sodium with biodegradable polymers, E-caprolactone. He concluded that the films showed good physical features and stability. They were proved non-toxic and resulted in appreciable bioavailability[39].

Cohen, R.G. *et al.*, (1997), investigated the potential for retinal toxicity associated with increased interlobular penetration following intensive topical, oral and combined administration of ofloxacin in rabbits. No evidence of retinal toxicity was detected by indirect ophthalmoscopy, electron retinography or histopathalogical examination. Their study suggested that intensive topical and oral ofloxacin administration does not cause retinal toxicity in rabbits despite achieving effective aqueous and vitreous humor antimicrobial concentrations[40].

Brodovsky, S.C., and Snibson, G.R., (1997), has reported that fluoroquinolones, especially of Ofloxacin, have become the antimicrobial agent of choice in the initial management of selected cases of bacterial keratitis[41].

Urtti, A. *et al.*, (1994), fabricated controlled drug delivery of timolol using end-plugged pieces of silicon tubing and studied the release of the drug *in vitro*. They also studied the ocular and systemic absorption of 0.5% timolol maleate from these devices in rabbits for 8 hour and compared with eye drop administration. It was concluded that controlled drug delivery is a viable alternative in improving the therapeutic index of open-angle glaucoma therapy with timolol[42].

Lee, V.H.L. *et al.*, (1994), investigated the influence of drug release rate on systemic timolol absorption from polymeric ocular inserts in the pigmented rabbit. The inserts tested were made of polyvinyl alcohol, hydroxy propyl cellulose, and partial ethyl ester of poly (vinyl methyl ether/maleic anhydride) approximately 89.4%w/w in all cases[43].

Sasaki, H. *et al.*, (1993), prepared disc type ophthalmic inserts of beta-blockers with various polymers and drug release from the inserts were investigated. Tilisolol and poly (2-hydroxypropyl methacrylate) were mainly used as models of beta-blocker and polymer for an ophthalmic insert. Release of tilisolol from ten different types of polymer inserts showed a variety patterns. The release of tilisolol from and HPM insert was examined under various conditions. Medium pH and medium temperature influenced release of drug from inserts. Various beta-blockers also showed controlled release from their HPM inserts[44].

Shanwany, E.L S. (1992), described the ocular delivery of pilocarpine from ocular inserts. Polymeric ophthalmic inserts containing pilocarpine hydrochloride were formulated with ethyl cellulose, cellulose acetate phthalate and Eudragit RL/RS 100 polymers using a casting technique. The inserts produced a typical time course of prolonged pulse entry of the drug into the eye[45].

Saettone, M.F. *et al.*, (1992), prepared a series of cylindrical ophthalmic inserts based on mixtures of PVA, glyceryl behenate and different polymers such as Xanthan gum, iota-carrageenan, HPMC, hyaluronic acid and containing pilocarpine nitrate by extrusion and were subsequently coated with a mixture of Eudragit RL and RS. The inserts were tested for *in vitro* release studies and for miotic activity in rabbits[46].

Chowdhary, K.P.R. and Naidu, R.A.S., (1991), prepared and evaluated the cellulose acetate films as rate controlling membranes for transdermal drug delivery. The films were prepared by casting on mercury surface and the films were evaluated for uniformity of thickness, tensile strength, water vapor transmission, drug diffusion and permeability characteristics[47].

Attia, M.A. *et al.*, (1988), investigated the disposition of dexamethasone in different eye tissues following the application of an ophthalmic suspension and ocular inserts. The disposition in the corneal tissue, which was rather poor relative to the conjunctiva and iris-ciliary's body in the case of the suspensions, was markedly enhanced through application of the drug in a film delivery

system. They showed that Eudragit and cellulose acetate phthalate-based films enhance the disposition of the drug in the aqueous humor at specific time intervals. They showed that ophthalmic film delivery systems bring a considerable increase in extent of drug absorption compared to the suspension dosage form[48].

Grass, G.M. *et al.*, (1984), examined the ocular delivery of pilocarpine from erodible matrices made of polymers like polyvinyl alcohol and carbomer – 934. The study examined the feasibility of sustaining the release of water – soluble drug, pilocarpine to the tear film. In *vitro* studies demonstrated significant prolongation of drug release from these systems. The *in vitro* results were supported by *in vivo* miosis studies in albino rabbits[49].

Gruneberg, R.N. *et al.*, (1988), evaluated the antibacterial activity of ofloxacin against a wide range of clinical bacterial isolates and compared with that of nalidixic acid, norfloxacin, endoxacin, and pefloxacin by determination of minimum inhibitory concentrations (MIC). They reported that ofloxacin was very active against enterobacterial, *Clostridium perfringens*, *Chylmida trachomatis* than other fluoroquinolones and showed similar activity against *Staphylococcus* species[50].

Bloomfield, S.E. *et al.*, (1978), made a comparative study on soluble gentamicin ophthalmic inserts as a drug delivery system with drop, ointment and subconjunctival routes of administration. The tear film studies showed that the soluble collagen gentamicin inserts gave highest concentration of the drug for the longest period in a convenient and a fashion[51].

Maichuk, Y.F., (1978), discussed therapeutic advantages of using soluble ophthalmic drug inserts made of polyacrylamide, ethyl acrylate using various drugs such as Neomycin Kanamycin and indoxuridine[52].

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