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AZITHROMYCIN-A NOVEL DRUG DELIVERY SYSTEM FOR OCULAR APPLICATION

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ABSTRACT

Azithromycin (AZT) is a macrolide antibiotic derived from and similar in structure to erythromycin. Oral administration of AZT is effective for the treatment of trachoma; however, topical formulations are difficult to develop because of the drug's hydrophobicity. The aim of this study is to formulate a novel topical ophthalmic delivery system of AZT. A major problem being faced in ocular therapeutics is the attainment of an optimal concentration at the site of action. Poor bioavailability of drugs from ocular dosage forms is mainly due to the tear production, nonproductive absorption, transient residence time, and impermeability of corneal epithelium. In addition to this, drugs that are hydrophobic or unstable at the pH comfortable in eye cannot be formulated as eye drops. Novel drug delivery systems could be some effective means of exploring the potential of such drugs.[1-4] The treatment of ocular surface infections with topical AZT is desirable in medicine because systemic exposure to the drug is limited.[7] Major topical formulation problems arise from the fact that AZT is hydrophobic and sparingly soluble in water at neutral pH.[5] Therefore, there is a need to design a novel drug delivery system, which could deliver the drug topically. Ocular inserts are polymeric systems into which the drug is incorporated as a solution (hydrophilic drug) or dispersion (hydrophobic drug) and molded as solid or semi-solid sterile preparations, of appropriate size and shape, designed to be inserted behind the eyelid or held on the eye and to deliver drugs for topical or systemic effect.

KEYWORDS: Azithromycin, Macrolide, Novel drug delivery system, Ocular application.

INTRODUCTION

The eye is a complex organ with a unique anatomy and physiology. The structure of eye can be divided into two main parts: anterior segment and posterior segment (Fig.1). Anterior segment of the eye occupies approximately one-third while the remaining portion is occupied by the posterior segment. Tissues such as cornea, conjunctiva, aqueous humor, iris, ciliary body and lens make up the anterior portion. Back of the eye or posterior segment of the eye include sclera, choroid, retinal pigment epithelium, neural retina, optic nerve and vitreous humor. The anterior and posterior segment of eye is affected by various vision threatening diseases. Diseases affecting anterior segment include, but not limited to glaucoma, allergic conjunctivitis, anterior uveitis and cataract. While, age-related macular degeneration (AMD) and diabetic retinopathy is the most prevalent diseases affecting posterior segment of the eye. Topical instillation is the most widely preferred non-invasive route of drug administration to treat diseases affecting the anterior segment. Conventional dosage forms such as eye drops account for 90% of the marketed ophthalmic formulations. The reason may be attributed to ease of administration and patient compliance.[8] Nonetheless, the ocular bioavailability is very low with topical drop administration.

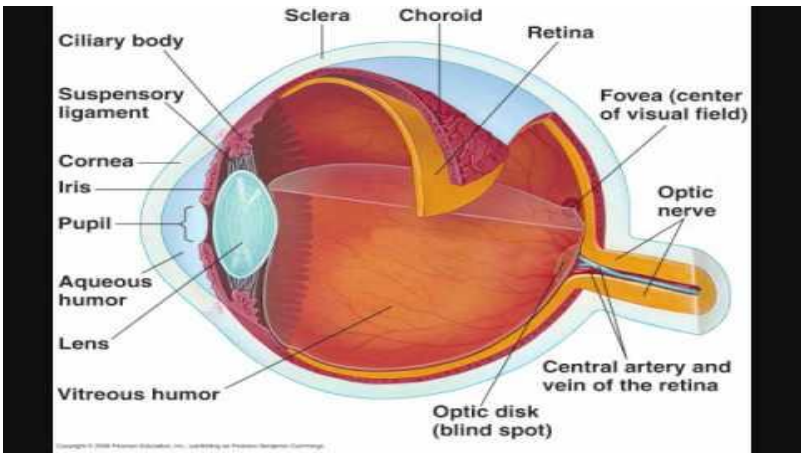

Fig. 1: Structure of eye.

Numerous anatomical and physiological constraints such as tear turnover, nasolachrymal drainage, reflex blinking, and ocular static and dynamic barriers pose a challenge and impede deeper ocular drug permeation.[9] Hence, less than 5% of topically applied dose reaches to deeper ocular tissues.[10] Also, it is difficult to achieve therapeutic drug concentration into posterior segment ocular tissues following topical eye drops instillation because of the above mentioned barriers. The drug can be delivered to the posterior segment ocular tissues by different mode of administrations such as intravitreal injections, periocular injections, and

systemic administration. However, small volume of eye compared to whole body and presence of blood retinal barriers; makes systemic administration an impractical approach. Intravitreal injection is the most common and widely recommended route of drug administration to treat posterior ocular diseases. Though, the need of repeated eye puncture with intravitreal injections causes several side effects such as endophthalmitis, hemorrhage, retinal detachment and poor patient tolerance.[11] The transscleral drug delivery with periocular administration route is evolved as an alternative mode of drug delivery to the posterior ocular tissues. Although transscleral delivery is comparatively easy, less invasive and patient compliant, drug permeation is compromised by ocular static and dynamic barriers. Ocular barriers to transscleral drug delivery include: static barriers *i.e.*, sclera, choroid and retinal pigment epithelium (RPE), and dynamic barriers, *i.e.*, lymphatic flow in the conjunctiva and episclera, and the blood flow in conjunctiva and choroid.[12,13]

To overcome the ocular drug delivery barriers and improve ocular bioavailability, various conventional and novel drug delivery systems have been developed such as emulsion, ointments, suspensions, aqueous gels, nanomicelles, nanoparticles, liposomes, dendrimers, implants, contact lenses, nanosuspensions, microneedles, and *in situ* thermosensitive gels for the earlier mention ocular diseases. This review will provide an overview on various conventional and novel ophthalmic drug delivery systems developed to deliver drug to diseased ocular tissues for the treatment of ocular diseases.

PHARMACOLOGY

Mechanism of action

Azithromycin prevents bacteria from growing by interfering with their protein synthesis. It binds to the 50S subunit of the bacterial ribosome, thus inhibiting translation of mRNA. Nucleic acid synthesis is not affected.

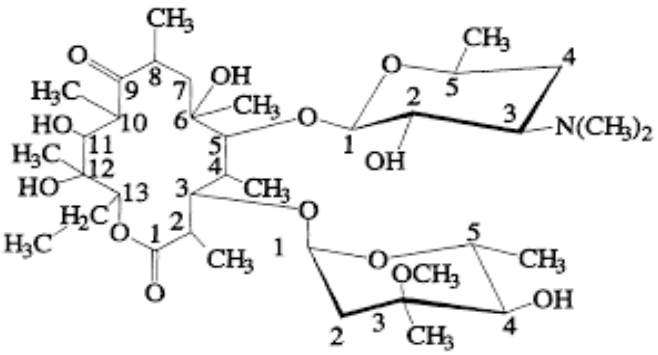

Fig. 2: Structure of Azithromycin.

IUPAC: **(**2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-11-[(2S,3R,4S,6R)-4-(dimethyl amino)-3-hydroxy-6-methyloxan-2-yl]oxy-2-ethyl-3,4,10-trihydroxy-13-[(2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyloxan-2-yl]oxy-3,5,6,8,10,12,14-heptamethyl-1-oxa-6-azacyclopentadecan-15-one.

Pharmacokinetics

Azithromycin is an acid-stable antibiotic, so it can be taken orally with no need of protection from gastric acids. It is readily absorbed, but absorption is greater on an empty stomach. Time to peak concentration (T_{max}) in adults is 2.1 to 3.2 hours for oral dosage forms. Due to its high concentration in phagocytes, azithromycin is actively transported to the site of infection. During active phagocytosis, large concentrations are released. The concentration of azithromycin in the tissues can be over 50 times higher than in plasma due to ion trapping and its high lipid solubility. Azithromycin's half-life allows a large single dose to be administered and yet maintain bacteriostatic levels in the infected tissue for several days.

Following a single dose of 500 mg, the apparent terminal elimination half-life of azithromycin is 68 hours. Biliary excretion of azithromycin, predominantly unchanged, is a major route of elimination. Over the course of a week, about 6% of the administered dose appears as unchanged drug in urine.

CONVENTIONAL OCULAR DRUG DELIVERY SYSTEMS

Topical drop instillation into the lower precorneal pocket is a patient compliant and widely recommended route of drug administration. However, most of the topically administered dose is lost due to reflux blinking and only 20% (−7 μL) of instilled dose is retained in the precorneal pocket.[14] Concentration of drug available in the precorneal area acts as a driving force for its passive diffusion across cornea. However, for efficient ocular drug delivery with eye drops, high corneal permeation with longer drug cornea contact time is required. Several efforts have been made toward improving precorneal residence time and corneal penetration. To improve corneal permeation ionophoresis, prodrugs, ion-pair forming agents and cyclodextrins are employed.[15-19] There is a wide range of ophthalmic products available in the market out of which around 70% of prescriptions include conventional eye drops. The reasons may be due to ease of bulk scale manufacturing, high patient acceptability, drug product efficacy, stability and cost effectiveness.

NOVEL OCULAR DRUG DELIVERY SYSTEMS

Nanotechnology based ocular drug delivery

In a last few decades, many approaches have been utilized for the treatment of ocular diseases. Nanotechnology based ophthalmic formulations are one of the approaches which is currently being pursued for both anterior, as well as posterior segment drug delivery. Nanotechnology based systems with an appropriate particle size can be designed to ensure low irritation, adequate bioavailability, and ocular tissue compatibility. Several nanocarriers, such as nanoparticles, nanosuspensions, liposomes, nanomicelles and dendrimers have been developed for ocular drug delivery. Some of them have shown promising results for improving ocular bioavailability.

Nanoparticles

Nanoparticles are colloidal carriers with a size range of 10 to 1000 nm. For ophthalmic delivery, nanoparticles are generally composed of lipids, proteins, natural or synthetic polymers such as albumin, sodium alginate, chitosan, poly (lactide-co-glycolide) (PLGA), polylactic acid (PLA) and polycaprolactone. Drug loaded nanoparticles can be nanocapsules or nanospheres. In nanocapsules, drug is enclosed inside the polymeric shell while in nanospheres; drug is uniformly distributed throughout polymeric matrix. From past few decades, nanoparticles have gained attention for ocular drug delivery and several researchers have made attempts to develop drug loaded nanoparticles for delivery to both anterior and posterior ocular tissues.

MATERIALS AND METHODS

Preparation of ocular inserts[20,21]

Films were prepared containing different ratios of Carbopol or alginate to HPMC. Ratio of plasticizer 50% weight per gram of total polymer weight was used (Formulation code F1-F8). A 2% w/v polymeric solution was prepared with water and combined with plasticizer, the solution was centrifuged for 20 min, and then casted onto a Petri dish and dried in an oven at 35°C until dry. The film was then removed from the Petri dish and cut to the required size. The films were stored in a glass container maintained at 25°C until use. Films with air bubbles or other imperfections were discarded. In manufacturing films containing Azithromycin, the drug was added to the polymeric solution before casting onto a Petri dish. Five polymeric inserts for each formulation/batch were fabricated. Dried inserts were then cut into oval-shaped inserts with the help of a sharp-edged die (13.2 mm in length and 5.4 mm in

width). Ocular inserts of the above-mentioned dimensions with an area of approximately 77 mm^2 were cut from the main insert, producing approximately 77 inserts for each batch. Each ocular insert contained theoretically 2.4 mg of the drug calculated on the basis of standard paper weight surface area method.[20, 22]

Drug release profile of Azithromycin ocular films

Formulation F8 was chosen as the optimized formulation on the basis of the longest span of drug release. Also, it has shown optimum physicochemical, mechanical, and bioadhesive parameters. Only formulation F8 was taken up for the kinetic modeling and ocular irritation studies. To determine the release mechanism that provides the best description to the pattern of drug release, the *in vitro* release data were fitted to zero-order, first-order, and diffusion-controlled release mechanism according to the simplified Higuchi model. The preference for a certain release mechanism was based on the correlation coefficient (*r*) for the parameters studied, where the highest correlation coefficient is preferred for the selection of the mechanism of drug release.

Successive evidence of the relative validity of diffusion and first order models was obtained by further analyzing the data using the following equation.

$M_t/M_\infty = K.t^n$

Where, M_t/M_∞ is the fraction released of the drug at time *t*, K is a constant incorporating structural and geometric characteristics and *n* is the release exponent characteristic for the drug transport mechanism. When $n = 0.5$, Fickian diffusion is observed and the release rate is dependent on t, whereas $0.5 < n < 1.0$ indicate anomalous (non-Fickian) transport and when $n = 1$, the release is zero-order. The optimized ocular insert F8 follows the first-order kinetics. Values of $n = 0.73$ of formulation supported an anomalous non-Fickian release. As known, $n = 0.5$ (indicating diffusion-controlled drug release) and $n = 1.0$ (indicating swelling-controlled drug release). Values of n between 0.5 and 1.0 can be regarded as for the superposition of both the phenomena (anomalous transport). Hence, in the present case, the drug release from the matrix is controlled by both phenomena, that is, diffusion and swelling.

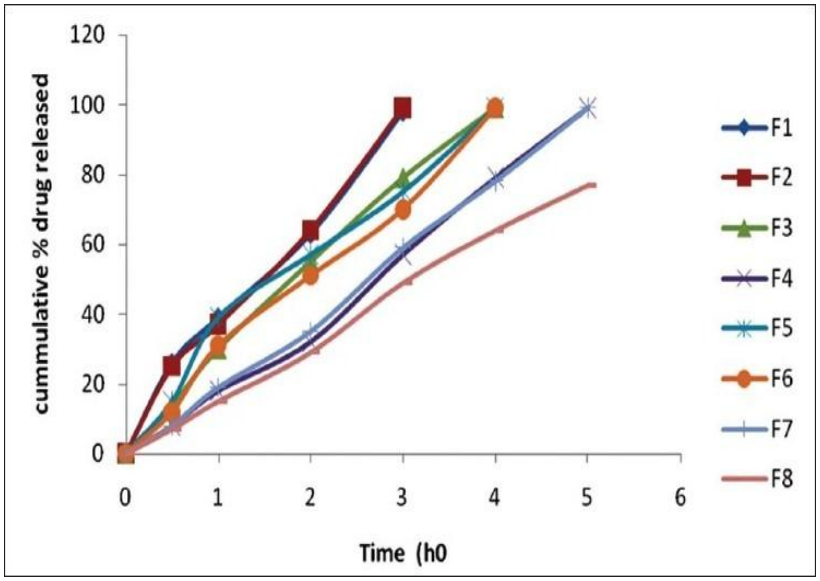

Fig. 3: Drug Release Profile of Azithromycin.

Physicochemical evaluation

Thickness of Insert [20,21]

Thickness of the inserts (n = 3) was measured using dead weight thickness gauge (Prolific). After initial settings, the foot was lifted with the help of the lifting lever fixed on the side of the dial gauge. Insert was placed on the anvil such that the area where the thickness is to be measured lies below the foot. Readings of the dial gauge were recorded after gentle lowering of foot.

Weight variation test [20,23]

Inserts from each batch were randomly selected and weighed individually on electronic balance (AND HR 2000). Mean weight of inserts (n = 20) of each formulation was recorded.

Surface pH determination [20,21]

Inserts were left to swell for 5 h on agar plate prepared by dissolving 2% (w/v) agar in warm simulated tear fluid (STF; sodium chloride: 0.670 g, sodium bicarbonate: 0.200 g, calcium chloride. $2H_2O$: 0.008 g, and purified water q. s. 100 g) of pH 7.4 under stirring and then pouring the solution into Petri dish till gelling at room temperature. After the time of soaking, the pH of the wet surface *was* measured by placing the electrode in contact with the surface of the insert.

Drug content uniformity [20,24]

Uniformity of the drug content was determined by assaying the individual inserts. Each insert was grounded in a glass pestle mortar and 5 mL of STF was added to make a suspension. The suspension so obtained was filtered and the filtrate was assayed spectrophotometrically at 225 nm (UV–VIS Shimadzu Spectrophotometer, India Ltd., India).

Mechanical strength

Ocular insert with good tensile strength and percent elongation would resist tearing due to stress generated by the blinking action of eye. The insert was cut into strips (50 × 10 mm). Tensile strength and elongation at break was determined by modifying the method used by Mishra and Gilhotra.[21] The apparatus consisted of a base plate with a pulley aligned on it. One aluminum clip was fixed on one end of the base plate, to which the insert (n = 3) was clipped. The other end of the insert was clipped to movable aluminum clip. A thread was tied to movable clip and passed over the pulley, to which a small pan was attached to hold weights. A small pointer was attached to the thread that travels over the scale affixed on the base plate. The weights were gradually added to the pan till the insert (that was affixed between two clips) was broken. The weight necessary to break the insert was noted as break force and the simultaneous distance traveled by the pointer on the scale indicated the elongation at break. The following parameters were calculated as per equations.

Tensile strength (g/mm^2) = break force (g)/cross-sectional area of the sample (mm^2)

Elongation at break (E/B) (%) = increase in length at break point (mm) ($L_s - L_o$)/original length (L_o) (mm) × 100.

Swelling index of ocular inserts

Swelling of the polymer depends on the concentration of the polymer, ionic strength, and the presence of water. To determine the swelling index of prepared ocular inserts (n = 3), initial weight of insert was taken, and then placed in agar gel plate (2% w/v agar in STF, pH 7.4) and incubated at 37°C ± 1°C. For 5h, insert was removed from plate after every 1 h, surface water was removed with help of filter paper, and insert was reweighed. Percent hydration was calculated.

Hydration % or (Sw) % = [wt – wo/wo] × 100

(Sw) % = equilibrium percent swelling, wt = weight of swollen insert after time t,

wo= original weight of insert at zero time

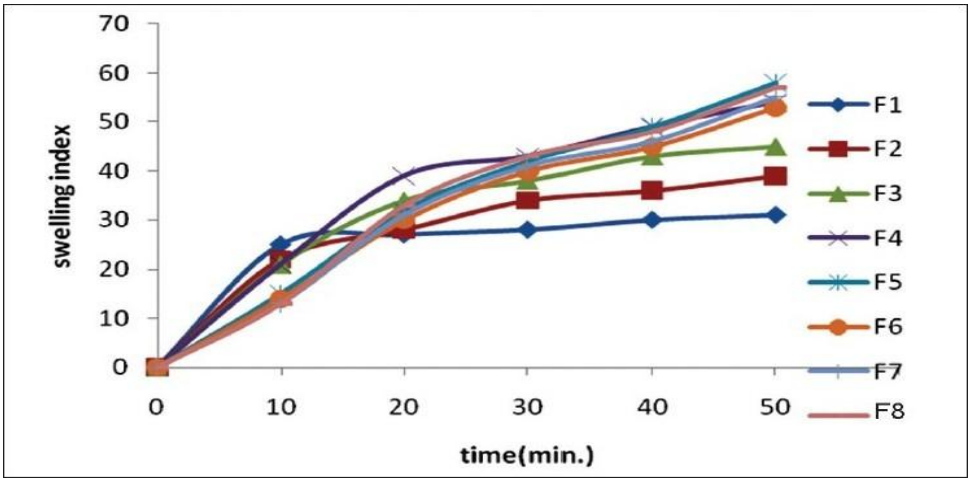

Fig. 4: Swelling index.

Stability study of azithromycin in ophthalmic preparations

A stability study of azithromycin in ophthalmic preparations was developed by submission to different types of light, temperature and pH, using the biodiffusion assay (cylinder 3 x 3) for the quantifications. *Bacillus subtilis*, ATCC 9372 was used as test organism. The used concentration range was of 50 to 100 µg/mL. The study demonstrated that the drug suffered degradation when submitted to the ultraviolet light, germicide light, solar luminosity, acid solution, basic solution and hydrogen peroxide solution. The results were analyzed by the analysis of variance (ANOVA).

DRUG DESCRIPTION

AzaSite (azithromycin ophthalmic solution) is a 1% sterile aqueous topical ophthalmic solution of azithromycin formulated in DuraSite® (polycarbophil, edetate disodium, sodium chloride). AzaSite is an off-white, viscous liquid with an osmolality of approximately 291 mosm/kg.

Preservative: 0.003% benzalkonium chloride. Inactives: mannitol, citric acid, sodium citrate, poloxamer 407, polycarbophil, EDTA, sodium chloride, water for injection, and sodium hydroxide to adjust pH to 6.3.

Precautions when taking azithromycin ophthalmic solution (Azasite)

Before using azithromycin, tell your doctor or pharmacist if you are allergic to it; or to other macrolide antibiotics such as erythromycin or clarithromycin; or to ketolide antibiotics such as telithromycin; or if you have any other allergies. This product may contain inactive

ingredients, which can cause allergic reactions or other problems. Talk to your pharmacist for more details.

Before using this medication, tell your doctor or pharmacist your medical history, especially of other eye problems.

After you apply this drug, your vision may become temporarily blurred. Do not drive, use machinery, or do any activity that requires clear vision until you are sure you can perform such activities safely.

How to apply the eye drops

1. Tilt your head back slightly and pull down your lower eyelid to create a small pocket. Hold the dropper above the eye with the tip down. Look up and away from the dropper and squeeze out a drop.
2. Close your eyes for 2 or 3 minutes with your head tipped down, without blinking or squinting. Gently press your finger to the inside corner of the eye for about 1 minute, to keep the liquid from draining into your tear duct.
3. Use only the number of drops your doctor has prescribed. If you use more than one drop, wait about 5 minutes between drops.
4. Wait at least 10 minutes before using any other eye drops your doctor has prescribed.
5. Do not touch the tip of the eye dropper or place it directly on your eye. A contaminated dropper can infect your eye, which could lead to serious vision problems.
6. Do not use the eye drops if the liquid has changed colors or has particles in it. Call your pharmacist for new medicine.
7. Use this medication for the full prescribed length of time. Your symptoms may improve before the infection is completely cleared.
8. Store an unopened bottle of azithromycin ophthalmic in the refrigerator. Do not freeze.
9. After opening the bottle, you may keep the medication at room temperature for up to 14 days. Keep the bottle tightly closed when not in use. Protect from moisture and heat.
10. Use the missed dose as soon as you remember. Skip the missed dose if it is almost time for your next scheduled dose. Do not use extra medicine to make up the missed dose.

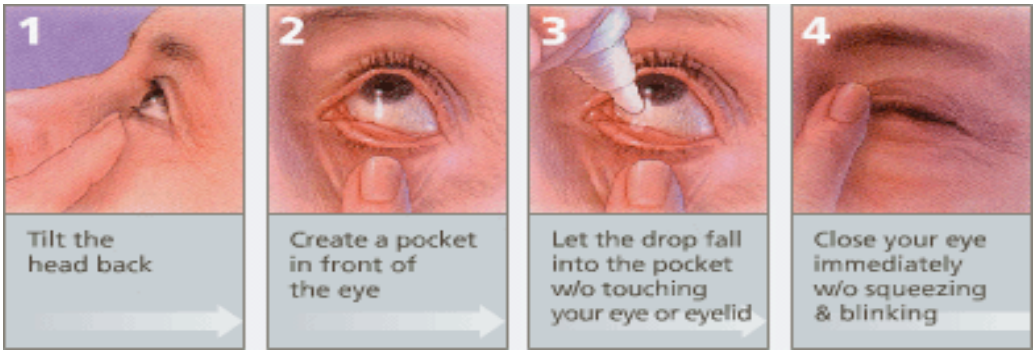

Fig. 5: Application of eye drops.

AZITHROMYCIN OPTHALMIC SIDE EFFECT

Get emergency medical help if you have any of these signs of an allergic reaction: hives; difficulty breathing or swallowing; swelling of your face, lips, tongue, or throat.

Stop using azithromycin ophthalmic and call your doctor at once if you have.

i Drainage or crusting of your eye;

ii Severe burning, stinging, itching, or other irritation after using the eye drops;

iii Feeling like something is in your eye;

iv Watery eyes, increased light sensitivity;

v Eye pain, redness, or swelling;

vi Any signs of a new infection; or

signs of a rare but serious reaction--fever, sore throat, swelling in your face or tongue, burning in your eyes, skin pain, followed by a red or purple skin rash that spreads (especially in the face or upper body) and causes blistering and peeling.

Common side effects may include

i Dry or itchy eyes;

ii Blurred vision;

iii Changes in your sense of taste

AZITHROMYCIN OPTHALMIC INTERACTION

Do not use this medication while wearing contact lenses. Azithromycin ophthalmic may contain a preservative that can discolor soft contact lenses. Wait at least 15 minutes after using azithromycin ophthalmic before putting your contact lenses in. You should not wear contact lenses while you still have active symptoms of the eye infection you are treating (eye redness, irritation, or drainage).It is not likely that other drugs you take orally or inject will have an effect on azithromycin ophthalmic used in the eyes. But many drugs can interact with

each other. Tell your doctor about all medicines you use. This includes prescription, over-the-counter, vitamin, and herbal products. Do not start a new medication without telling your doctor.

AZITHROMYCIN OPTHALMIC DOSAGE

Azithromycin ophthalmic is usually applied twice daily for 2 days, and then once daily for 5 more days. Use exactly as prescribed by your doctor. Do not use in larger or smaller amounts or for longer than recommended. Follow the directions on your prescription label. Wash your hands before using the eye drops.

RESULTS AND DISCUSSION

The present investigation was undertaken with the objective of preparing a sustained release bioadhesive ocular insert of Azithromycin using alginate, carbopol, and HPMC as the matrix former as well as bioadhesive polymers. Propylene glycol (PG) was employed as plasticizer in the preparation to get inserts/films with good elasticity. The film casting procedure followed to prepare formulations resulted in the preparation of uniform Azithromycin-polymeric bioadhesive inserts. The drug was dissolved in the polymeric solutions prior to casting. The concentration of the polymers plays an important part in the preparation of the polymer matrix. The solution of the insert was kept at room temperature for 24 h to enhance interdiffusion of polymer particles. Upon drying, polymer solutions were converted into drug polymer inserts/films. Various research groups have studied the mechanism of film formation using polymer dispersions. The film formation occurs in 3 stages.

(a) Evaporation of the casting solvent and subsequent concentration of polymer particles,

(b) Deformation and coalescence of polymer particles, and

(c) Further fusion by interdiffusion of polymeric molecules of adjacent polymer particles.

The physical state of the drug in the dried polymer is dependent on the solubility of the drug in the polymer. In the present case, the drug was dispersed in the polymeric solution. The success of film formation method is further evident from the fact that the prepared inserts/films were translucent, colorless, and smooth in texture, uniform in appearance, thickness, and weight and showed no visible crack or imperfection. As a general observation, carbopol films (without HPMC) were highly elastic and sticky. Each ocular insert had an area of approximately 77 mm^2. The insert had a thickness varying from 0.045 ± 0.007 mm to 0.055 ± 0.003 mm. The dimensions of first ever commercially available ocular insert OCUSERT® system by ALZA Corporation, Palo Alto, California; the Pilo-20 system is 5.7 ×

13.4 mm on its axes and 0.3 mm thick; the Pilo-40 system is 5.5 × 13 mm on its axes and 0.5 mm thick. The prepared formulations were rather thinner than the commercially available ones, indicating their physiologic suitability. The weight of the prepared formulation varied from 6.97±0.44 to 7.50±0.21 mg. The drug content was consistent in all batches and varied from 97.9% ± 0.1% to 99.8% ± 0.4%.

CONCLUSION

The complications in eye formulation are mainly due to specific anatomical and physiological features of eye. The development of in-situ stimuli activated gel-forming systems for ophthalmic drug delivery provides simplest and best gel-forming systems. It is an ideal system that maintains effective level of drug for the longer duration following a single application and offers the primary requirement of a successful controlled release product that increases patient compliance.

Moreover, various polymers used in this system provide advantage over conventional drug delivery system. Most of the currently marketed ocular drugs were initially developed for non-ocular applications. Recently, tremendous research is carried out to make orally available drugs applicable for topical ocular therapeutically effective by the help of polymer system fabrication. Azithromycin can be developed as an ocular insert delivery system for the treatment of ocular surface infections. The ocular delivery system of Azithromycin based on carbopol and HPMC has shown a sustained drug release as well as good ocular stability. This dosage form is a good means of making the hydrophobic drug, which is topically delivered. The development of Azithromycin in this delivery system could enhance the antibiotic's usefulness in ophthalmology for the topical treatment of ocular surface bacterial infections and lid margin diseases. Further work to check the therapeutic potential of the dosage form *in vivo* is in progress.

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