

A Review on Herbal Ophthalmic Preparations

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Abstract: Nature has always provided an unlimited source of biologically-active compounds. Controlled interventional examinations have shown that drugs of animal origin and plant extracts could be utilised safely. Ocular medications such as eye drops or an ointment are used to treat and prevent eye diseases. Growing evidence that plant extracts and animal tissues have anti-inflammatory, wound-healing, antibacterial, antioxidant, anticancer, and anti-angiogenic effects has stimulated greater study investment. Many traditional herbal eye drops prepared from many medicinal plants combination, could cure ophthalmic disorders. This review briefly explains about herbal eye drops.

Keywords: *Herbal eye drops, Ocular medication.*

INTRODUCTION:

In many parts of the world medicinal plants have been used as traditional treatment for many human diseases for thousands of years. Herbal remedies are still the main source of medication in rural areas of underdeveloped nations. Herbal eye drop is a polyherbal formulation used for anti-inflammatory, antihistaminic effect and degenerative ophthalmic disorders. Biswas et al. reported that many traditional herbal medicines used in curing ocular diseases are now being gradually increased in modern medicine science.[1] The herbal eye drop formulation is prepared for beneficial effects in allergic and inflammatory conditions of the eyes. For treatment of eye ailments the herbal drugs used dates to the days of Rigveda, Bhrigutantra, Asvini kumara, Charaksamhita and Sushrutsamhita. The W.H.O has revealed the importance of herbal cures and it has been active in creating guidelines and standards of botanical medicine. [2] The therapeutic impact of medicinal plants in ocular problems was recorded in several in-vitro trials and animal investigations. The primary uses of ocular drugs, such as eye drops or an ointment, are the treatment and prevention of eye conditions. When we refer Ayurvedic classics for therapeutic measures adopted for the treatment of eye diseases, many topical treatments along with some systemic ones are observable. The difficulties of systemically delivered medications to traverse the blood's aqueous, intraocular, and retinal blood barriers may be the reason why topical therapy are preferred. The topical measures play a pivotal role and are called as 'Kriya Kalpas'. Sushruta the father of Indian Ophthalmology mentioned six Kriya Kalpas.- Tarpana, Putapaka, Seka, Aschotana, Anjana, Arka.[3]

THERAPIES FOR EYE DISORDERS IN ANCIENT TIMES:

Seka: Fomentation with decoction of Kanthakari (*Solanum xanthocarpum*) root, prepared with milk. Fomentation with concentrated extract of either Nagarmotha (*Cyperus scariosus*) or Sendha Namak (Rock Salt) or Mulethi (*Glycyrrhiza glabra*) or Pippali (*Piper longum*) prepared with milk.

Anjan: Paste of Mulethi (*Glycyrrhiza glabra*), Harida (*Curcuma longa*) Harad (*Terminalia chebula*) Devdaru (*Cedrus deodara*), in equal parts prepared with goat milk or water and concentrated. An Anjan (Collerium) is prepared and applied.

Arka: Steam distillates of plants like Punarnava (*Boerhavia diffusa*), Palash (*Butea monosperma*), and Mulethi (*Glycyrrhiza glabra*), used as eye drops.

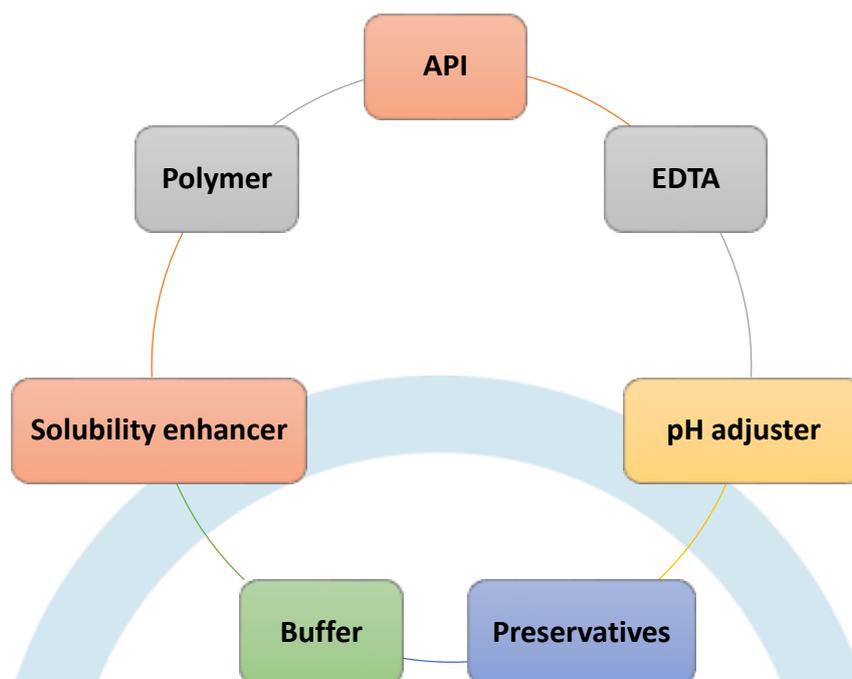
Paste: Fine paste of drugs used as ointment.

Washing: Washing of eyes with extract of drugs like Triphala comprising of three drugs viz. Amla (*Embica officinalis*), Harad (*Terminalia chebula*) and Bahera (*Terminalia belerica*)[3]

Eye Drop: There are a number of factors that contribute to eye conditions, including mucous membrane scarring, inadequate glycoprotein production, and underactive lacrimal glands. Eye drop are sterile or suspensions of drugs that are implanted in to the eye with a dropper. They usually contain drugs having antiseptic, anti-anesthetic, anti-inflammatory, mydriatic or meiotic properties.[4] Since the retinal tissue weighs in milligrammes and has a limited surface area, despite being extremely vascular, the eye only receives a little part of the cardiac output. Direct delivery of medication to the eye is desirable, especially when using well-established topical methods like eyedroppers.[5] The optimum volume for a drop delivered to the eye is estimated to be between 5 and 20 μ L.

BASICS FOR FORMULATIONS HERBAL EYE DROPS:

The formulator must have a good awareness of anatomical and physiological factors in addition to the understanding of control of solubility, sterility, stability and material properties in cocktails of compositions. Owing to limitations of different conventional agents it is at this juncture that the need for safe and effective drugs that could effectively tackle dry eye syndrome. Scientific confirmation of the safety and efficacy of the numerous indigenous medications paired with the numerous claims of their diverse uses in treating a wide variety of ocular diseases is required. More than forty metal minerals and more than fifty ophthalmic plant



Medications with a variety of pharmacological effects on the eye's adnexa and visual system are mentioned in Ayurvedic literature.[6,7] Yastimadhu (*Glycyrrhiza glabra* Linn.) & Daruharidra (*Berberis aristata* DC.) are some of such medicinal plant sources having potential leads in the management of surface ocular inflammatory conditions such as dry eye syndrome, supported by textual references from Ayurvedic literatures backed by experimental and clinical studies. When Daruharidra (*Berberis aristata*) was applied topically and orally, the subjective dryness, redness, photophobia, and other dry eye syndrome symptoms significantly improved.[8] Pharmacological actions such as caksusya (conducive to vision), netrya (conducive to adnexa of eye), netraruja-hara (analgesic ophthalmic action), netrasodhahara (anti-inflammatory action) netrakanduhara (anti allergic action), vranaropana (wound healing effect) are attributed to these drugs.[9,10] Yastimadhu (*Glycyrrhiza glabra*) has shown notable anti-inflammatory action attributed to cortisone-like substance present in this plant that helps reduction of inflammation.[11] It is clear that the combination of substances, Yastimadhu (*Glycyrrhiza glabra*), and Daruharidra (*Berberis aristata*), contribute to the total care of dry eye syndrome by restoring the functions of the tear film, preventing ulceration and related suppressing inflammatory process.[12] The eye drops is formulated with these two plant ingredients and developed as per Indian Pharmacopoeia (IP, 1996) complying quality standards and other parameters such as isotonic to lacrimal fluid, particulate matter, pH, Sodium chloride content, sterility test besides permissible e preservatives and packing specifications etc.[13,14]

TOPICAL OPHTHALMIC FORMULATION INGREDIENTS:

The extracts of herbal products and Ayurvedic, Siddha and Unani formulations are mixtures of at least partially uncharacterized constituents. It is claimed that such a mixture provides a therapeutic advantage, since the unknown constituents may be additive or synergistic in action or may produce a balance to counteract adverse effects of any one constituent. This may provide more efficacy than the known constituent used alone.[15] Raw ingredient of various plants is used for formulation. The identity is confirmed with compliance of microscopic, macroscopic parameters of Ayurvedic pharmacopoeia of India (API) through pharmacognosy studies. The purity and strength were also confirmed through physicochemical studies done as per, Protocol For Testing of ASU Drugs (2008), Pharmacopoeia Laboratory for Indian Medicine, Ministry of AYUSH, Govt. India 17 and compliant with parameters of Ayurvedic pharmacopoeia of India (API).[16]

Tonicity:

Lacrimal fluid is an ultra-filtrate that is produced from a glandular discharge that is isotonic with blood. Its ability to neutralise unbuffered solutions is partly due to the contributions of protein and the body's bicarbonate-carbon dioxide system and is due to the mixture of electrolytes, weak organic acids, and protein that it contains. Addition of tonicity agents allows formulations to be formulated to have tonicities equivalent to the range 0.7 to 1.5% w/w sodium chloride.[17]

Salts:

Because it takes a combination of ionisable and lipophilic nature to pass the epithelium and the stroma, the majority of ophthalmic medicines are weak bases or weak acids (to partition into the epithelium). For acidic drugs such as NSAIDs, the sodium and tromethamine salt have been used.[18] Indomethacin is unstable in alkaline solution and poorly soluble below pH 6 and therefore may be preferentially presented as a suspension in polyvinyl alcohol (PVA) or HPMC or solubilised in an oil-in-water suspension. Flurbiprofen base is practically insoluble in water and presented as the sodium salt at a pH 6–7 0.03% concentration, and solutions at a concentration of greater than 0.2% are reported to be quite irritant. Generally, drug solutions contain a high concentration to try and drive transcellular absorption through the cornea. According to reports, flurbiprofen permeation increases when the preservative benzalkonium chloride is present because ion pairs form and the solution turns opalescent.[19]

Buffers:

Alkaloids are often more chemically stable in acidic solutions, and using a mild buffer enables the lacrimal fluid to raise the pH, increasing the amount of medication that is unionised and available for absorption. Tear film pH recovery after instillation of a drop is largely due to tear turnover.[20] and buffer strength directly impacts patient sensation of eye comfort. For this reason it is desirable that the buffers used in ophthalmic formulations are weak. Another consideration is autoclaving, stability and the effect of pH.[21] The degradation of solutions at elevated temperatures is significant for labile compounds. Atropine for example is stable at 25 °C with a half-life of 2 years at pH 6.8 and 130 years at pH 5. When heated to 121 °C, the degradation is much faster: 1 hour at pH 6.8 and 60 hours at pH 5. [17]

Preservatives:

A multi-dose preparation that is in use will quickly lose its sterility and put the patient at hazard. Facial organisms, especially *Staphylococcus aureus*, will colonise non-preserved formulations with ease.[22] A multi-dose container has preservatives added to it to promote stability and try to stop bacterial development during the in-use cycle.[23] The most commonly used modern preservatives are perborates, polyquads and oxy-hypochlorites (Purite). Borate has mild antimicrobial activity and 1.2% w/v borate at pH 7 has inhibitory activity against the growth of *Staphylococci* and *Pseudomonas* sp.[24] Benzalkonium chloride (BKC, BAK) is probably the most commonly used of the polyquad preservatives and is an effective bactericide and fungicide. It is a mixture of alkylbenzyl dimethylammonium chlorides of different alkyl chain lengths, from C8 to C18, but mostly C12 and C14.[25] The mercury-based preservatives like thimerosal, which increased the effectiveness of a preparation containing chloramphenicol and neomycin sulphate, are older preservatives that are no longer commonly used. Other examples include chlorhexidine, sorbic acid or sorbates, benzchlorobutanol, and sorbates.[26] The very old mercurials phenylmercuric acetate and phenylmercuric nitrate have almost disappeared. Parabens are still found in some preparations but their use is decreasing. The similarity of nasal and ophthalmic mucosa dictates that similar formulations are used for both routes. An excellent series of reviews on antimicrobial preservatives was published by Elder and Crowley.[27] Ethylenediaminetetracetic acid (EDTA) increases the effectiveness of preservatives since it chelates Ca^{2+} and Mg^{2+} needed for bacterial or fungal metabolism. It has been demonstrated to have minimal toxicity in a number of combinations, and it disrupts the plasma membrane and generally increases cellular permeability, producing effects that are comparable to those of BAK but milder in developed corneal cells.[28] In combination with a high molecular weight hyaluronic acid, these deleterious effects seem to be reduced.[29]

Hydrotropes:

Originally described by Neuberg in 1916, a hydrotrope increases the solubility of a compound through a non-micellar mechanism. In most cases, relatively significant amounts of the chemical are used in comparison to the API, and solubilisation occurs by changing the structure of water and the creation of solute-hydrotrope complexes, which might involve completely enclosing the drug.[30] In reality, this is nanomicellization.

Polymers:

The use of polymers in ophthalmic preparations has been reviewed by Calles. [31] And by Wagh[32] The most important factors to take into account when choosing polymers are their filterability, stability for heat sterilisation, and compatibility with the other formulation components. Polyvinyl alcohol is also a widely used drug delivery vehicle and a component of artificial tear preparations. This polymer can reduce interfacial tension at the oil/water interface, enhancing re-wetting of the surface. Therefore, polymeric solutions are useful components in the replacement of mucin-deficient tears in postmenopausal dry eyes.[33] Finding polymers that adhere to mucin or mucous-covered membranes, such as the conjunctivae or cornea, and stay in contact with the precorneal tissues until the surface mucin is turned over, is a typical objective in ophthalmic formulation.[34] In this context, the narrower term “mucoadhesion” is employed. The polymer tails must be long enough and mobile to facilitate molecular entanglement. The threshold has been defined as around 100 000 Da in flexible chain motif polymers. The highest interaction between anionic polymers and surface mucins occurs at an acidic pH, indicating that the polymer must be in its protonated form for viscoelastic synergy with mucins. Additionally, combinations of several phase-transition polymers are being researched in an effort to enhance gelling characteristics while simultaneously lowering the overall polymer payload in the system, enhancing tolerability and lowering discomfort. Simple mixing sometimes produces synergistic effects on thickening but may result in reduced mucoadhesion.[17]

Lipid-Based Emulsions:

Lipid-based emulsions are presented as three types: oil-in-water emulsions (most common), water-in-oil emulsions and bicontinuous lipid emulsions.[35] The emulsions are stabilised with a suitable surfactant. Pharmaceutical emulsions such as Restasis, an anionic lipid emulsion containing 0.05% cyclosporin, established an important toe-hold in treatment of chronic dry eye and subsequently a number of cationic lipid emulsions, including Cationorm[®] and Novasorb[®], were launched for treatment of dry eye disease.[36] Nano-emulsions and liposomes are two examples of the more recent oil-based systems that fall within the category of lipid-based nanocarriers.[37] A positive charge on a liposome formulation markedly decreases clearance in rabbits compared to negatively charged or neutrally charged liposomes.[38] Other candidates for ophthalmic emulsions include ester forms of drugs such as flurbiprofen.

Suspensions:

The preferred dosing vehicle is usually a solution but stability in dilute solutions may limit shelf life. Particle size is important because particles 15 µm or larger are irritants. Accordingly, typical specifications are 95% average particle size below 10 µm. It

goes without saying that milling to create smaller particles will create a chance for a sustained delivery based on control of the rate of disintegration.[39] Due to the larger depot, larger particles should potentially prolong the effects; yet, there is a chance of irritation and suspended particles being washed out before dissolving, resulting in decreased bioavailability. Issues arise when suspensions are left because of cyclical exposure to heat and cold, which may induce crystal development and sedimentation on the bottom of the dropper bottle. Suspensions are kinetically stable but thermally unstable as a system, and problems occur when left. It is therefore important that the particle is in a deflocculated state.[40]

Table 1. Summary of substances of natural origin with their corresponding activity in ocular tissues.

Natural Source	Extract / Isolated Compound	Pharmacological Properties	Reference
Liquorice	glycyrrhizin	Anti-inflammatory	[41]
Daruharidra	berberine	Antiseptic	[41]
Achyranthis radix	Aqueous extract plant	Cytoprotective, anti-inflammatory	[42]
Coffea arabica	Caffeine	UV protection, Antiangiogenic	[43,44,45,46]
Cannabis sativa	Δ^9 -THC	Ocular hypotensive effect Neuroprotection	[43]
Aloe barbadensis Miller	Aqueous extract of Aloe vera	Wound healing Anti-inflammatory Immunomodulatory	[43]
Yastimadhu	Aqueous extract of dried root	Anti-inflammatory	[47]
Berberis aristata DC.	Aqueous extract of Dried stem	Anti-allergic Anti-inflammatory	[47]
Jasminum officinale	Jasmine oil	Anti-inflammatory analgesic	[48]
Zingiber officinale	Ethanollic extract of Rhizome	Anti-inflammatory	[49]
Cedrus deodara	Aqueous extract of Bark	Anti-inflammatory analgesic	[50]
Cyperus rotundus	Rhizome	Anti-inflammatory	[51]
Terminalia chebula, Terminalia bellirica, Phyllanthus emblica,	Ethanollic extract of Triphala	Antimicrobial Antioxidant.	[52]
Emblica officinalis	Aqueous extract of Fruit	Cataract	[53]
Trigonella foenum	Aqueous extract of Seed	Cataract	[53]
Cheilanthes glauca Terminalia chebula	Aqueous extract of plant	Cataract	[53]
Butea Monosperma	Aqueous extract of Flower	Cataract	[54]
Honey and Rose water	Aqueous extract of flower	Cunjunctivitis	[55]

METHODOLOGY:

Since ophthalmic products are sterile products, the processes and procedures used in production are essentially similar to those for parenteral administration. Manufacturing must be done in a clean environment with strict adherence to the preservation of quality features and lack of contamination. The eye drop are prepared in four stage.

Preparation of Bacterial And Fungicidal Vehicle: The aqueous or oily vehicle is used in preparation of eye drops. The aqueous vehicle may support bacterial or fungal growth. So one of the following bactericide may be used to prepare the eye drops: a) phenyl mercuric nitrate / acetate - 0.002%, b) benzalkonium chloride – 0.01%, c) Chlorhexidine -0.015

Preparation of Solution of Medicaments and Adjuvant: The medicament are dissolved in the aqueous vehicle containing suitable anti-microbial agent. The adjuvants are also dissolved in the vehicle at a stage to form a stable preparation.

Clarification: The eye drops are clarified solution is immediately transferred in to final containers and sealed to exclude micro-organisms.

Sterilization: The eyes drops are sterilized by autoclaving or heating with bactericide at 98° to 100° C for 30 mins or filtration through bacteria proof filter.

FORMULATION DEVELOPMENT:

- The step wise development of eye drops encompasses the preparation of distillate, making of the distillate isotonic to lacrimal fluid and adjustment of pH, addition of preservative and packing under sterile conditions.
- All coarsely powdered drugs were soaked in distilled water for overnight in a beaker.
- And then transferred to a distillation unit. Distillate was obtained by adjusting the temperature to 40⁰C for 15 minutes and raising the temperature slowly to 80⁰C. The first 450 ml of distillate was collected at the rate of 20 drops per minutes in an airtight container.
- 0.9 % NaCl was selected as vehicle and 2.5% of extract was added.
- The distillate was made isotonic to lacrimal fluid by adding 0.9% NaCl to distillate and dissolving properly and adding isotonic phosphate buffer viz.0.16g of monobasic Sodium phosphate and 0.76g of dibasic Sodium phosphate.
- Finally, the pH of the eye drops was adjusted to 6.9 - 7.30. Benzalkonium chloride was added as preservative and pH was again checked and found within the specified range of the ophthalmic drops (pH 6.9-7.30).
- Test for sterility performed after addition of preservative the preparation was observed for 48 hours and found sterile.
- The packing was made in autoclaved sterilized amber glass containers of 10 ml. Capacity
- The finished product tested for quality assurance and safety and the analytical specifications complied specified parameters of Indian pharmacopeia for ophthalmic preparations.[56,57]

EVALUATION OF HERBAL EYE DROP PREPARATION:

The side effects are believed to be less with herbal preparations, though there are very few systematic studies conducted to evaluate this. The present study intended (i) to evaluate the protective effect of a specific preparation of Ayurvedic eye drops and (ii) to assess whether the Ayurvedic eye drops themselves would cause irritation or not. The rabbits were allocated to experimental and control groups. The experimental group had 3 sub-groups and the control group had 6 rabbits. The experimental group was given the test substance for 28 days daily. The control group was kept in the same environmental conditions without any treatment. Each 10 ml of the Ayurvedic preparation is considered. The test substance was instilled in the conjunctival sac of the left eye of each animal in the experimental group after pulling the lower lid away from the eyeball. The subgroups were (i) the low dose group, consisting of those rabbits which were given 0.1 ml per day for 28 days; (ii) intermediate dose group, which consisted of those rabbits which were given 0.1 ml twice a day for 28 days; and (iii) those rabbits which were given 0.1 thrice a day for 28 days, who were tagged as the high dose group. All assessments were blind scored. Irritation of the eye was assessed on day 7, 14, 21 and 28 using an ocular lesion scale which consist of three parts, part 1 measured opacity (degree of density), part 2 was to check the reaction of the iris (pupil) to light and part 3 was to measure the redness of the palpebral and bulbar conjunctiva, cornea and iris, and to measure chemosis.

Assessed Results: Eye irritation, Haematological tests, Biochemistry tests, Organ weight, Necropsy tests, Histopathological tests. [58]

Evaluation of Raw Herbs:

Pharmacognostic and Phytochemical evaluation of herbs are Tests for carbohydrates, Tests for proteins, Tests for Amino Acids, Tests for alkaloids [58, 59], Tests for tannins, Tests for flavonoids.

Thin layer chromatography:

Sample preparation: - Preparation of stationary phase: - TLC plates were taken, Silica gel G was dissolved and poured on the plate then the plate was dried in oven at 105⁰C for 30 minutes. Mobile phase preparation: - Toluene: ethyl acetate: Diethylamine was took in the ratio (7:2:1) for alkaloid and Toluene: acetone: Formic acid (4.5:4.5: 1) was took for tannins.

Evaluation by physico-chemical tests:

Determination of ash value:

$$\% \text{ Ash} = \frac{\text{weight of crucible} - \text{weight of empty crucible}}{\text{Weight of sample}} \times 100$$

Determination of acid insoluble ash:

$$\% \text{ Acid insoluble ash} = \frac{100(M2-M1)}{M1-M}$$

Where, M2 = lowest mass in gm of dish with acid insoluble ash, M1 = Mass in gm of empty dish, M = Mass in gm of dish with dried material.

Determination of water-soluble ash:

$$\% \text{ Water soluble ash} = \frac{\text{weight of water} - \text{soluble ash}}{\text{Weight of sample}} \times 100$$

Formulation and Development of herbal eye drop:

Three different batches were prepared for the formulation containing different concentration of the ingredients.[60,61]

Evaluation of Finished product:

1. Organoleptic properties: Colour, Odour, Appearance, Texture.

2. Physico-chemical parameters of finished product: Determination of pH, Determination of density, Isotonicity, Determination of Viscosity was done with Ostwald viscometer.

$$n_2 = p_2 t_2 n_1$$

$$p_1 t_1$$

Where, n_1 = viscosity of std liquid, p_1 = Density of std liquid, t_1 = Time required by std liquid, n_2 = Viscosity of test liquid, p_2 = Density of test liquid, t_2 = time required by test liquid.

Determination of Surface tension with Stalagmometer and drop count method was done

$$r_2 = \frac{p_2 n_1 r_1}{p_1 n_2}$$

Where, n_1 = Number of drops of std liquid, n_2 = number of drops of test liquid, p_1 = density of std liquid, p_2 = density of test liquid, r_1 = surface tension of standard liquid, r_2 = surface tension of test liquid.

Sterility testing: The product was made sterile in autoclave at 121°C and 115 psig for 15 mins. [62]

Stability Studies:

Long-Term and Accelerated Test: The long-term and accelerated test was carried out by storing formulation in 25 ± 2 °C/ 60% \pm 5% RH and 40 ± 2 °C/60% \pm 5% RH for 4 weeks to measure the several parameters including content change of ecdysterone and formation of the precipitate. The sterility test was conducted using fluid thioglycolate medium and soybean-casein digest medium to confirm the absence of the aerobic and anaerobic bacteria and fungi. A total of 1 mL of 1% USL was transferred into 12 mL of media. Then, the media were incubated at 32°C and the growth of micro-organisms was observed for 14 days.

Compatibility Test The compatibility test: In the compatibility test, 1% USL and each additive were stored together at 40°C oven for 4 weeks.

Thermal Stability Test: The stability of the formulation against heat was evaluated. Each formulation was assessed for transmittance by measuring the amount of precipitate formed at 121 °C for 30 min.[63]

RECENT ADVANCES IN AYURVEDIC OPHTHALMIC DRUG DELIVERY SYSTEM:

Viscosity Modifiers: Polymer forms a back bone of a dosage form developed to prolong the precorneal residence time of topically applied drugs. First attempt made to prolong the contact time of applied drug with cornea was to increase the viscosity of the preparation. The viscosity modifiers used were hydrophilic polymers such as cellulose, polyvinyl alcohol and poly acrylic acid. Polysaccharides such as xanthan gum were found to increase the viscosity and delay the clearance of the instilled solution by tear flow. Herbal drugs of various solubility incorporated into these polymers to form gels. According to Patton and Robinson, the maximum increase in ophthalmic drug corneal penetration would occur at viscosities of about 15 to 150 cp. Further increases in viscosity are associated with blurred vision and resistance to eyelid movements. These polymers have high molecular weights and cannot cross biological membranes. Greaves et al., reported that formulation of polymers that display non newtonian properties offer significantly less resistance to the eyelid movements. Viscosity of vehicles increases contact time but there is no marked sustaining effect.[64]

Mucoadhesive Polymers: Goblet cells in the cornea secrete glycoprotein which forms a thin film over cornea called as mucin. Mucin is capable of holding about 40-80 times its weight in water as it consists of very large linear peptide chain to which large number of oligosaccharide chains are bound. The application of natural and synthetic polymers known as mucoadhesive polymers which will adhere to mucin and stay in the area of mucin as long as it is evident for attractive medication delivery. Robinson observed that polyanions are better in bio adhesiveness and toxicity as compared to polycations in terms of bio adhesion. A wide variety of polymers are accessible, and several researchers have provided methodologies to quantify the bio adhesion of such polymers. Following mucoadhesive polymers are used most of the times in various ophthalmic drug delivery systems.

Polyacrylic Acid:

Carbopol:

Cross linked polyacrylic acid to have excellent mucoadhesive properties causing significant enhancement in ocular bioavailability. Carbopol 934 P is high cross link water swell able acrylic polymer with molecular weight approximately 3000000 Da. which is appropriate to use in pharmaceutical industry. Park Robinson and Ponchel et al. reported that poly acrylic acid interact with functional group of mucus glycol protein via carboxylic group. Precorneal residence of carbopol solution found to be greater than that of PVA solution when Davis et al. evaluated corneal clearance of pilocarpine in carbopol 934P solution compare to that of end equiviscous non mucoadhesive PVA solution and buffer (PBS) in the rabbits. Saettone et al. carried out much experiment with pilocarpine, the poly acrylic acid (5% w/v) carbopol 941P form a stable precorneal film and with less solubility. Drug duration of stable film effect significantly increases as compare to pilocarpine. Weinreb et al. found that suspension beta hexabol base on the poly acrylic acid provided a more constant release of betaxolol than its solution. Thermos et al. evaluated ocular bioavailability of timolol in isoviscous solution of PVA (PAA and timolol PAA salt). The result suggested that PAA polymer produce lower ocular concentration than those after PVA and slower the release of timolol. and resulting in longer retention of vehicle in conjunctival sac by mucoadhesion. [33] Use of carbopol in ophthalmic drug delivery having following advantages and disadvantages: Gel prepared for ophthalmic administration using carbopol are more comfortable than solution, or soluble inserts though they are instilled like ointment less blurring of vision occurred as compare to ointment. However, disadvantages are no rate control on drug instability and it leads to matted lids.[65]

Polycarbophil:

It is cross linked poly acrylic acid polymer which is insoluble in water but swells and can incorporate large quantity of water. Carbophil cross linked with divinyl glycol found to give good bio adhesion as compare to conventional non bio adhesive suspension.

Carboxymethyl Cellulose: Sodium CMC found to be excellent mucoadhesive polymer. Ophthalmic gel formulated using NaCMC, PVP and corbopol on the in vivo studies on the gel showed diffusion coefficient in corbopol 940 1% > NaCMC 3% > PVP 23%. Recent research suggests that adhesive strength increases as molecular weight increases up to 100000 da.

In-Situ Gelling Systems: In early eighty's concept of in situ gelling come existence these systems will have low viscosity and will be instilled as eye drops and will change in to gel like system when in contact with corneal fluid. This sol to gel transition can be brought about by three ways. Change in temperature, change in pH and ion activation. pH triggered system: When in contact with tear fluid with a pH of 7.2 to 7.4, cellulose acetate hydrogen phthalate latex normally has very low viscosity up to pH 5 and forms a clear gel in a matter of seconds, releasing its contents over an extended period of time. Use of such pH sensitive latex described by Gurny the half-life of residence of CAP dispersion on corneal surface was approximately 400 seconds as compare to 40 second for solution [38]. However, this system is associated to discomfort to patient due to high polymer conc and low pH of instilled solution.

Change in Temperature: When Poloxamer F127 is injected into the eye, a phase shift from solution to gel takes place at the temperature of the eye, extending its contact with the ocular surface. Poloxamer F127 is a solution at room temperature. Pluronic polyol represent a class of block copolymer consisting of (polyoxyethylene and polyoxypropylene units). No of these units and their ration per mol of polymer provide wide range of polyol with different physical and chemical properties.

Ion Activation: Gelrite is a polysaccharides, a low acetyl gellan gum shows phase transition in presence of mono or divalent cations. Timolol bioavailability found to be superior with gelrite over equiviscous HEC solution.[66]

Colloidal systems: Main object in optimization of ocular drug delivery is to increase the contact time of drug with conjunctiva. The effectiveness of colloidal carriers such liposomes nanoparticles in extending corneal contact time has led to increased testing of ocular medication delivery. Smolin for the first time studied application of liposome for ocular drug delivery. Liposomal suspension of idoxuridine found more efficient in the presence of herpex simplex keratitis in rabbit as compare to idoxuridine solution [44]. Similarly significant increase of triamcinolone in aqueous humor found from the administration of encapsulated trimcinolone in liposomes. However, result after administration of pilocarpine 0.1 % in liposomes in terms of intraocular pressure found disappointing when compared with pilocarpine isotonic buffer solution. Same result obtained with dihydrostptomycin sulphate after administration in the form of liposomes. Ion activation: Gelrite is a polysaccharides, a low acetyl gellan gum shows phase transition in presence of mono or divalent cations. Timolol bioavailability found to be superior with gelrite over equiviscous HEC solution. Colloidal systems: The primary goal of optimising ocular drug delivery is to prolong the period that the drug is in contact with the conjunctiva. Since liposomes nanoparticles were discovered to be helpful in extending corneal contact time, they are being studied more and more for application in ocular medication delivery. Smolin for the first time studied application of liposome for ocular drug delivery. Liposomal suspension of idoxuridine found more efficient in the presence of herpex simplex keratitis in rabbit as compare to idoxuridine solution. Similarly significant increase of triamcinolone in aqueous humor found from the administration of encapsulated trimcinolone in liposomes. However, result after administration of pilocarpine 0.1 % in liposomes in terms of intraocular pressure found disappointing when compared with pilocarpine isotonic buffer solution. Same result obtained with dihydrostptomycin sulphate after administration in the form of liposomes. Liposomes than lipophilic drugs [49]. Charge on liposomes also influence drug concentration in ocular tissues [50]. Positively charged liposomes boost medication concentration in ocular tissue, whereas negatively charged mucin covers the negatively charged corneal epithelium, according to all authors.

Ophthalmic Insert: Ophthalmic insert defined as sterile preparation with solid or semisolid consisting and whose size and sharp are especially designed for ophthalmic application.^[56] They provide a number of benefits over aqueous solutions, including increased ocular residency, the ability to release drugs at a slow, steady rate, precise dosing, and a longer shelf life. Two types of Ocuserts® are available in the market [57]. Various polymers tried in ophthalmic inserts were polyacrylic acid, polyvinyl alcohol, silicone elastomer, hydroxy propyl cellulose, ethyl cellulose cellulose acetate phthalate and polymethacrylic acid, hyaluronic acid. It has also been suggested in the literature that biopolymers, such as fibrin and chitosan, could be used to create soluble or erodible inserts.

Ocular Iontophoresis: Ocular iontophoresis offers drug delivery system that is fast pain less safe and result in delivery of high conc of drug to specific site[59]. Studies on ocular iontophoresis of 6-hydroxydopamine and methyl para tyrosine carried by number of investigators. Iontophoresis application of antibiotics may enhance bactericidal activity of the antibiotics and reduce the severity of the disease.[67]

CONCLUSION:

The use of botanical eye drops offers eco-friendly control strategy to aid the pathological issues. Various herbs based ophthalmic products has been the most accepted bio-products, due to the presence of multiple beneficial Phyto-constituents in their plant extracts and it not only provides a sustainable control mechanism but also prevents worsening of the condition, due to various

synthetic products. The herbal eye drops developed certainly contribute significantly in the management of eye syndrome. This review helps the researcher to develop new formulations for eye disorders, which will be beneficial for the society in future era.

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