OCULAR INFLAMMATION AND NSAIDS: AN OVERVIEW WITH SELECTIVE AND NON-SELECTIVE COX INHIBITORS

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Abstract: Inflammation is a complex biological response and like other parts of the body, ocular inflammation could have untoward effects on vision if not detected and/or diagnosed early. NSAIDs are the major ocular therapeutics for treating such eye inflammations and preferred over corticosteroids. NSAIDs are given orally as well as topically to treat ocular inflammations, however topical route is preferred over systemic route for treating such conditions. To further decrease the adverse effects caused by NSAIDs due to their non-selective nature, preferential cyclooxygenase-2 (COX-2) inhibitors are preferred over non-selective cyclooxygenase (COX) inhibitors. The present review covers various facets of NSAIDs in ocular drug delivery for treating ocular inflammatory condition.

Keywords: Ocular inflammation, NSAIDs, Cyclooxygenase, Topical ocular delivery

1. INTRODUCTION

Inflammation is an immediate complex biological response of the body that occurs often due to invading parasite or tissue injury triggered by chemicals, or physical stress [1-2]. Hence, a defensive response wherein altered physiological reactions limit tissue damage and expelled out pathogenic substances or abnormally generated self-compounds produced during tissue injury [3-4]. Acute inflammation is a short-term response characterized by vasodilation, infiltration of leukocytes at infected region with a rapid resolution phase and repair of the damaged tissue. Therefore, inflammation executed beneficial activities against acute infection and injury. In contrast, chronic inflammation is the state of prolonged and uncontrolled inflammatory reactions. As inflammatory mediators are not specific to particular tissue targets, chronic inflammation could be a common etiological and physiological factor for various chronic conditions like allergy, atherosclerosis, arthritis, cancer and several autoimmune diseases [2-3, 5].

Eye is a delicate organ supplied with highly responsive nerves. The inflammation process in eyes is similar to rest of body organs and usually encounter in postoperative incidences especially after cataract surgery. Post-operative inflammation includes disrupted blood-aqueous barrier, conjunctival hyperaemia, miosis, increased intra-ocular pressure (IOP), mediated by COX pathways [6]. These conditions, if left untreated, can lead to visual impairment and blindness. Hence, the treatments of ocular inflammatory conditions are quite necessary for protection of vitality of vision. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been reckoned as an efficient modulators of ocular inflammatory reactions as they inhibit prostaglandin biosynthesis, the major product of COX pathway [7]. This review solely focuses on NSAIDS mechanism and regulation as selective and non-selective COX inhibitors for various ocular inflammatory conditions.

2. OCULAR INFLAMMATION AND PHARMACOTHERAPEUTICS

Majorly depending on the tissues, the inflammation of eye can be divided in these parts (Figure 1).

2.1. Conjunctiva

It is a translucent mucous membrane that delineates the posterior surface of the eyelids and anterior of eyeball. Inflammation of conjunctiva (conjunctivitis) [8] includes infective conjunctivitis (bacterial, chlamydial or viral), allergic conjunctivitis and granulomatous conjunctivitis [8].

2.2. Cornea

Cornea is a transparent, avascular, watch glass like structure that forms anterior one-sixth of the outer fibrous coat of the eyeball. Inflammation of the cornea (keratitis) includes ulcerative keratitis and non-ulcerative keratitis [8].

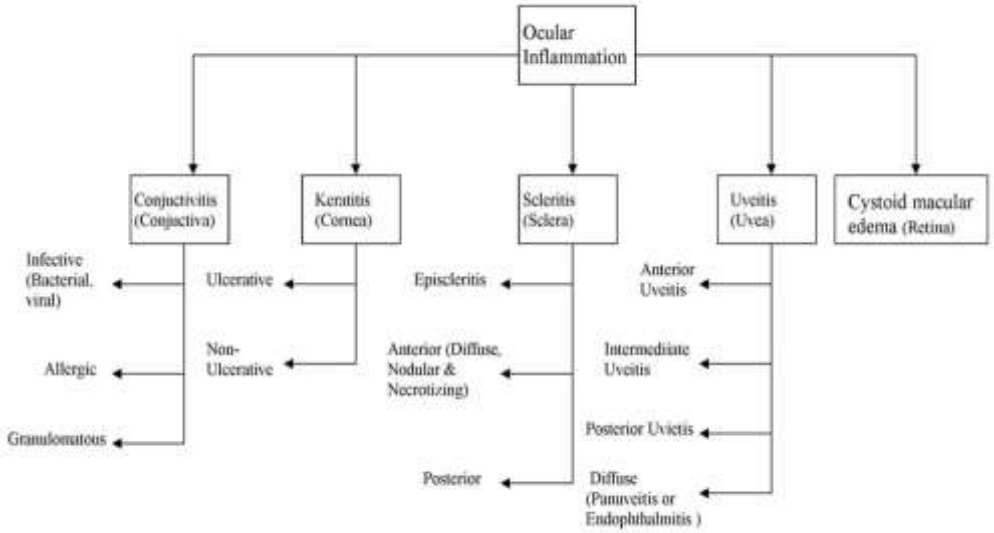

Fig. 1. Various ocular inflammatory diseases

2.3. Sclera

Sclera forms the posterior 5/6th part of the external fibrous tunic of the eyeball. Inflammation of sclera is known as scleritis. It is a systemic inflammatory or infectious disorder. Symptoms of scleritis include red eye, blurred vision, eye discomfort, eye pain, red patches on the whites of the eyes, tearing of the eye, and photophobia. It is further divided into epicscleritis, anterior Scleritis (diffuse, nodular and necrotizing with/without inflammation) and posterior scleritis [9].

2.4. Uveal tract

Uveal tissue constitutes middle vascular coat of the eyeball and divided into iris, ciliary body and choroid. Uvea provides nutrition to various part of eye such as cornea, lens, retina, and vitreous. Symptoms of uveitis (uveal inflammation) include light sensitivity, pain, blurring of vision and redness. The major inflammations are anterior uveitis (inflammation of the iris alone), intermediate uvietis (Ciliary body), posterior uveitis (Choroid) and it may be diffuse involving all parts of uvea (panuveitis/endophthalmitis). Additionally there is degeneration of iris and choroid with some tumors of choroid, ciliary body and iris [10].

2.5. Retina

Cystoid macular edema (CME) is a painless condition affecting macula (central retina). This condition is characterized by multiple cyst like areas of fluid that appears in the macula leading to swelling which finally results into blurred and distorted vision [11-12].

The various ocular inflammatory conditions have been effectively treated with anti-inflammatory drugs like corticosteroids and non steroidal anti-inflammatory (NSAIDs).

Corticosteroids

Corticosteroids are one of the important therapeutics for inflammation suppression though possess serious side effects like alteration of lipid, protein and carbohydrate metabolism and other enzymatic reactions, susceptibility to infection, hypertension, muscle weakness. Hence, use of steroid is indicated for short term treatment only and for specific inflammatory process [13]. In market various corticosteroids such as cortisone acetate (0.5% suspension and 1.5% ointment), hydrocortisone (0.5% suspension and 0.2% solution), dexamethasone sodium phosphate (0.1% solution and 0.5% ointment), medrysone (1% suspension) etc. are available [14]. However, administration of these steroids for therapy of ocular inflammation usually associated with various adverse effects. Ocular side effects of steroid therapy are generally observed with its systemic administration. For example, subcapsular cataracts and papilledema occured after prolonged systemic administration of prednisolone and triamcinolone respectively [13]. Apart from systemic administration, topical delivery of steroids too affect eye adversely. Incidence of keratitis

(bacterial, fungal and/or viral) was observed with the use of topical or sub-conjunctival corticosteroids. Similarly, galucoma, pupil dilation, blurred vision, occasional refractive changes, lens opacities, and ptosis were noted following topical corticosteroid administration. In few cases, relapse of ocular inflammation was observed on rapid or abrupt discontinuation of topical ocular steroid use. These side effects often become prominent on prolonged administration but could be avoided with short-term use (less than 3-4 weeks) [13-15].

Non-steroidal anti-inflammatory drugs

For management of ocular inflammatory conditions, NSAIDs are preferred over corticosteroids due to improved safety profile as they are deprived of steroid related adverse affects [6, 16-19]. Moreover, these anti-inflammatory drugs are imperative in pre and post operative inflammation. [20-21]. Though NSAIDs have an edge over corticosteroids, still posses certain side effects like blurred vision, dry eye, diplopia, retinopathy etc (Table I) [22-30]. These could be attributed to their low solubility which makes them difficult to dispense in aqueous solution. However various formulation technologies such as solubilization, cyclodextrin complexation, nanoemulsion, liposomes, niosomes, ocular inserts, hydrogels etc. have been emerged as a solution for such difficulties.

3. NSAIDs

3.1. Ophthalmic indications

NSAIDs act by irreversibly blocking cyclo-oxygenage (COX) enzyme. COX enzyme is essential for the synthesis of prostaglandin (conversion of arachidonic acid to prostaglandins). Additionally they also block lysosomal enzymes,

TABLE I
Characteristics of various NSAIDs with topical side effects [22-30]

NSAID		Solubility	Protein binding (%)	Topical side effects	Novel systems improving drug characteristics
Aspirin	1.46	1.43	80	Periorbital angioedema	Iontophoresis, Polymeric nanoparticle
Indomethacin	0.0024	3.4	97	Stromal opacities, Retinopathy	Polymeric nanoparticle, hydrogel inserts, microemulsion
Ibuprofen	0.0068	3.5	99	Blurred vision, diplopia, dry eye	Nanostuctured lipid carrier, Polymric nanosuspension
Naproxen	0.05	3.29	99	Intracranial hypertension	Bioerodible implant, polymeric nanoparticle
Ketoprofen	0.02	3.29	99	Blurred vision	Sloid lipid nanoparticles
Flurbiprofen	0.025	3.57	99	Exacerbated ocular tissue bleeding	Nanoemulsion, polymeric nanosuspension
Diclofenac	0.0045	4.98	99	Corneal erosion	Polymeric nanoparticle, Solid lipid nanoparticle
Piroxicam	0.06	1.81	99	Eye pain, blurred vision	Microsphere, nanosuspension
Ketorolac	0.051	2.66	99	Transient stinging and burning	In-situ gel, hydrogel inserts, polymeric suspension & micelles
Nimesulide	0.019	2.56	>90	Transient ocular irritation	Polymeric nanoparticle
Meloxicam	0.016	2.15	99.4	Corneal opacification	Thermogel
Celecoxib	0.005	3.99	97	Corneal opacification	Polymeric microsphere
Aceclofenac	0.015	2.17	99	Transient stinging and burning	Polymeric insert & polymeric nanoparticle

kinin system, lymphokinase and thromboxane thus inhibiting inflammatory response. Many NSAIDs are available for systemic administration but only a few marketed formulations are available for topical administration viz. indomethacin (0.1% suspensions), diclofenac sodium (0.1% solution), flubiprofen sodium (0.03% solution), nepafenac and ketorolac (0.5% solution). Ocular indications of various NSAIDs are discussed hereafter.

3.1.1. Scleritis

If left untreated, scleritis might lead to vision loss. NSAIDs are the first line of therapy for non-infectious scleritis [31]. Flurbiprofen and indomethacin have been found to effectual in such cases [31-33].

3.1.2. Cystoids macular oedema

NSAIDs are efficient in treating CME induced after post cataract surgery [20, 34]. Topical formulation of flurbiprofen, bromfenac [35], indomethacin and ketorolac have been found to be very effective in prophylactic treatment of CME following cataract surgery [18, 36]. Adding up to this, NSAIDs have also been effective in vitreoretinal surgery induced CME [18].

3.1.3. Uveitis

It is well treated inclusively by NSAIDs. The morbid attacks are markedly reduced by cellecoxib in patients associated with recurrent acute anterior uveitis (AAU) [37]. Infliximab could be helpful in the management of refractory juvenile idiopathic arthritis-associated uveitis [38].

3.1.4. Prevention of surgically induced miosis

FDA has approved suprofen (1%) [10] and flurbiprofen (0.03%) [39] intraoperative use to prevent miosis during cataract surgery [18]. Moreover, diclofenac [40] and ketorolac [41] have also been proved to be effective.

3.1.5. Postoperative inflammation

After various ocular surgeries such as cataract [42-44] glaucoma, strabismus and vitreoretinal surgery, there is induction of inflammation and these inflammations are finely treated by NSAIDs [45-48].

3.1.6. Postsurgical refractive surgery and postoperative trauma and discomfort

For the pain induced after refractive surgery such as radial keratotomy and excimer laser photorefractive keratectomy, ketorolac tromethamine [49-51] and diclofenac [52-56] are approved by FDA. Furthermore 0.1% nepafenac and 0.09% bromfenac have also been valuable [50, 57].

3.1.7. Conjunctivitis

Topical formulation of ketorolac (0.5%) [58-61] has been approved by FDA for seasonal conjunctivitis (allergic) with 0.1% diclofenac and 0.09% bromfenac. Various NSAIDs such as aspirin [62], indomethacin (1%), ketorolac (0.5%) [63], diclofenac (0.1%) [64], and bromfenac (0.09%) [65] treat vernal keratoconjunctivitis (bilateral chronic inflammation of the conjunctiva) that might lead to blindness [66]. Clinically NSAIDs have proved worthy in giant papillary conjunctivitis and hay fever [67-68]. Viral induced inflammation of conjunctiva is well controlled with ketorolac (0.5%) and indomethacin (0.1%) [69].

3.1.8. Orbital pseudotumor (idiopathic orbital inflammation)

Orbital pseudotumor is an orbital mass lesion characterised by infiltration of soft tissues by distinct inflammatory cells and fibrosis [70-71]. Oral indomethacin has been found to be effective in such cases [72].

3.1.9. Inflamed pinquecula and pterygia

Pinquecula is a yellowish patch on the site closest to nose. It is essentially not a tumor but deposition of protein and fat resulting alteration of tissue**.** Pterygia is an abnormal condition in which conjunctiva grows into cornea. Topical indomethacin provides dramatic relief in such conditions [73-74].

3.1.10. Diabetic retinopathy

In diabetic retinopathy there is swelling, leakage of fluid and damage of blood vessels of cornea**.** There is insufficient evidence supporting role of NSAIDs in such cases nevertheless 0.1% nepafenac and 0.09% bromfenac might be effective [75-76].

3.1.11. Ocular tumors

NSAIDs has been found to be very effective as chemotherapeutic agents in colon cancer**.** COX-2 selective NSAIDs have huge potential to restrain

tumors associated with such kind of tumor of eyes [77].

3.1.12. Age-related macular term degeneration (AMD)

It is the disease associated with growing age destroying sharp central vision and involves macula. There are insufficient evidence but huge potential of involving NSAIDs treating such cases that is established in various prospective studies [78].

4. MECHANISM OF INFLAMMATION AND COX-2 VS. NON-COX SELECTIVE NSAIDS

Cyclooxygenage (COX) enzyme is essential for the synthesis of prostaglandin (conversion of arachidonic acid to prostaglandins). The COX enzyme exists in at least two isoforms. COX-1 is a constitutive or "housekeeping" isoform that is responsible for the basal production of prostaglandins, prostacyclins, and thromboxanes (Figure 2). COX-2 is inducible by cytokines and other inflammatory stimuli and is believed to predominate during chronic inflammation. The final product of the COX pathway is tissue specific. Most of the NSAIDs inhibit not only inflammation induced synthesis of prostaglandins (PGs,) but also the production of the much smaller amounts of PGs required for the mediation and modulation of physiological processes. NSAIDs act by irreversibly blocking COX enzyme. In addition to this, they also block lysosomal enzymes, kinin system, lymphokinase and thromboxane thus inhibiting inflammatory response. Cyclooxygenage enzyme is mainly divided into constitutive COX-1 and inducible COX-2. Among NSAIDs preferential cyclooxygenase-2 (COX-2) are preferred over non selective cyclooxygenase inhibitors due to their selective nature for inducible COX-2 [27, 79-80].

Fig. 2. Role of COX-1 and COX 2 in inflammation

Ocular inflammation is similar to other body inflammation having common symptoms of hyperemia, protein exudation, pain and cellular response. Inflammation induced PGs have shown vasodilation in rabbit eyes and disruption of blood aqueous barrier [81]. In a uveitis induced model increased concentration of cyclooxygenase and 5-lipoxygenase products have been observed in the anterior chamber [81-84]. In an experimental model of experimentally induced uveitis in rabbit showed 60 fold increases in PGE_2 concentration in aqueous humour. This increased concentration was completely alleviated by dexamethasone that is a selective inhibitor of COX-2, suggesting that inflammation induced cyclooxygenase was majorly responsible for the inflammation of eyes and inflammatory PGs [85]. Few other experiments have supported this report showing role of COX-2 in ocular inflammation [86-88].

5. CURRENTLY AVAILABLE NSAIDS FOR TOPICAL ADMINISTRATION

Topical ocular delivery of NSAIDs has always been a preferred mode of drug administration to achieve high therapeutic concentration in eye and to avoid systemic side effects [89]. Various topical applications of NSAIDS have been explored by many researchers which led to many successful ocular products. These have been discussed below (Table II) [90-93].

Table II
Various NSAIDs and their specificity for COX enzyme [90-93]

Drug	COX-1 IC_{50} specificity (µM)	COX-2 IC_{50} specificity (µM)	COX-1 IC_{50}/COX-2 IC_{50}
Aspirin	342	>5000	<0.068
Indomethacin	6.7	164	0.008
Nepafenac	82.3	>1000	<0.08
Ketorolac	0.0139	0.0911	0.15
Bromfenac	0.0864	0.0112	7.71
Diclofenac	0.6	0.04	15
Flurbiprofen	0.018	0.00062	29.03
Amfenac	0.138	0.00177	77.96

5.1. Aspirin

Aspirin, a salicylic acid derivative, is a non-selective reversible COX inhibitor and available in market as oral tablets and suppositories

(Bayer®, Ecotrin®, St. Joseph®, Bufferin®, Anacin®, Excedrin®) [20, 94]. However the drug has been found clinically effective after topical ocular application. Aspirin is effective in vernal keratoconjunctivitis and prevents the progression of severe diabetic retinopathy [20, 95]. Patient taking aspirin have fewer chances to develop neovascular age-related macular degeneration [20]. In allergic conjunctivitis (pollen-induced) topically administered aspirin (1%) eye drops are established to be efficacious and safe [96]. Clinically few other indications have been reported such as delayed progression of cataracts by inhibiting aldose reductase by aspirin [97]. Gupta et al. proved effectiveness of 0.3 % w/v solution of aspirin lysine in prevention of galactosemic cataract in rats [98]. As topical delivery aspirin alone could not achieve a significant therapeutic concentration in posterior segment of eye, an iontophoretic method has been developed to achieve higher concentration to circumvent systemic side effect following IV administration [99].

5.2. Indomethacin

Indomethacin is an indole acetic acid derivative. It is available in market as 0.1% Indocollyre® eye drops and indicated for certain surgical ocular operations and post-operative inflammation (such as prevention of inflammation postoperatively cataract surgery, surgery of the anterior chamber of the eye) or inhibition of miosis during surgery. Its activity has also been confirmed in prevention of pain and inflammation that are produced after refractive surgeries. Clinically topical indomethacin has shown significant improvement in inflamed pinquecula and pterygia [20]. In a current study topical 0.1% indomethacin and 0.5% ketorolac have shown similar therapeutic effect in few ocular pre and post operative surgical conditions [20, 100]. Also 1% indomethacin is found to be effective in angiographic cystoid macular edema (CME) with improved effectiveness when it was used concurrently with corticosteroids [101-102]. Oral indomethacin have revealed competence in various ocular diseased cases including orbital myositis [72]. Klein et al. have found indomethacin to because statistically significant decrease in the incidence of aphakic cystoid macular edema [103].

As indomethacin has very low water solubility so dispensability and precipitation are the major concern. To overcome this problem various formulation approaches have been explored. Oily solution of indomethacin (1%) have shown significant higher aqueous humour penetration than indomethacin (1%) suspension with improved ocular bioavailability and prolonged action [104]. Nanoemulsion system (o/w) has been found to be an effective tool for delivery of indomethacin showing higher corneal permeability in animal studies [105]. Other nanotechnology such as nanocapsules, nanoparticles and nanosupesions have also been explored by various research groups [106-107]. As indomethacin is very susceptible to hydrolysis, nanocapsule systems restrain their hydrolysis in various physiological systems [108]. Such nanocapsules systems have also depicted intratumoral bioavailability and reduction in the growth of implanted gliomas showing effective possibilities in ocular tumor cases [109]. Chitosan based nanocarrier systems (nanoparticles and nanoemulsion) provide prolong indomethacin precorneal residence time to improve bioavailability for management of post-operative inflammation and intraocular irritation after cataract extraction. Such systems exhibit gradual release and high long-term therapeutic drug level in external and internal ocular tissues [110]. *In vitro* studies have shown high drug loading and sustained release of indomethacin from indomethacin-loaded poly(butylcyanoacrylate) nanoparticles forecasting a prolonged action [111]. Balasubramaniam *et al.* (2003) developed in situ gelling system of indomethacin to reduce pre-corneal drug elimination. Gelrite gellan gum that gels in presence of mono and divalent cations (present in lacrimal fluid) was used as in situ novel ophthalmic vehicle. This system sustained drug release over 8 hour and pharmacodynamic therapeutic efficacy was verified using uveitis induced rabbit model [112]. Various implants of indomethacin, such as implants with sodium alginate alone or in hydroxypropylmethylcellulose with or without calcium chloride have been made for controlled release of drug [113]. Film type scleral implants of indomethacin based on gellan gum [114] and sodium alginate [115] have also been formulated that have therapeutic efficacy of 2 and 3 weeks respectively.

5.3. Ketorolac

Ketorolac, an aryl acetic acid derivative, is a non selective COX inhibitor. Intrinsically it is 6 times more active for COX-1 than COX-2 [116]. Dextrorotatory isomer (d) of the drug shows twice

anti-inflammatory activity than the levorotatory (l) isomer [104]. Commercially it is available as tromethamine salt for ocular application (Acular® eye drops 0.5%, Acular Ls® Solution 0.4%, Centagesic® eye drops 0.5%). Clinically the drug (classified as ophthalmic decongestants) is used for the reduction of ocular pain, burning/stinging (following corneal refractive surgery), temporary relief of ocular itching, treatment of postoperative inflammation in patients who have undergone cataract extraction and reduction of ocular pain and photophobia (following incisional refractive surgery). Sandoval *et al.* found that 0.4% ketorolac tromethamine [61, 117] had similar effectiveness in reducing inflammation as 0.5% ketorolac tromethamine in reducing inflammation after routine cataract, post refractive and other surgeries [118-119] suggesting to use low doses in such cases. Ketorolac goes acid and base catalyzed autooxidation in buffered solution. Unbuffered solution of pH 6.5 endow with maximum stability for ocular delivery [120-121]. Moreover preservation of ketorolac aqueous drops with benzalkonium chloride (0.01%w/v), disodium edetate (EDTA) (0.01%w/v), chlorbutanol, phenylmercuric acetate and phenylmercuric nitrate are associated with increased stability and corneal permeation through rabbit cornea [122].

Keeping in view the auto-oxidative nature of drug in aqueous phases, oily solution and ointment had been developed. Ketorolac 0.2% showed maximum goat transcorneal permeability in sesame oil followed by formulations in corn oil and soyabean oil [123]. Partitioning of drug in oily and aqueous phase was responsible for cumulative release. Also permeability of ketorolac ointment was proved to be better than aqueous solution. Ketorolac drops (0.2%) formulated in sesame oil and soybean oil exhibited enhanced ocular bioavailability in rabbits when compared with ointment and aqueous formulations [124]. Moreover, ointment provides longer precorneal residence time. Aqueous humour $t_{1/2}$ of ketorolac was 10 hour with ointment and 6.6 hour with oil drops. Ketorolac ocular inserts were formulated using HPMC or methylcellulose and Povidone as polymeric films, with ethylcellulose film as rate controlling membrane (reservoir type of system). The ocular inserts developed using HPMC (4%) and ethyl cellulose (3%) was found to sustain ketorolac tromethamine release by zero order kinetics for 22 hour [125]. Gupta *et al.* (2000) studied ketorolac N-isopropylacrylamide, vinyl pyrrolidone and acrylic acid based copolymeric nanoparticles for enhance bioavailability of ketorolac [126]. Spherical nanoparticles (size of 35 nm) depicted two fold more *in vitro* release than aqueous suspension. Pharmacodynamic evaluation of nanoparticle formulation in PGE2-induced ocular inflammation in rabbits displayed a significantly higher anti-inflammatory activity in comparison to the aqueous suspension, which has been attributed to the small size of the particles and mucoadhesiveness. The nanoparticle formulation did not show any corneal damage during *in vitro* studies [127].

5.4. Bromfenac

Bromfenac, a bromine acetic acid derivative, indicated for the inhibition of inflammation after postoperative cataract surgery. Bromfenac is preferential COX-2 inhibitor. It is marketed in USA as Xibrom® solution**.** Waterbury *et al.* (2006) found 32 times more selectivity of bromfenac for COX-2 than COX-1 [116]. In animal model, both ketorolac 0.4% and bromfenac 0.09% demonstrated maximal anti-inflammatory activity in treated eyes however some systemic absorption is always possible. Bromfenac 0.09% ophthalmic solution rapidly clears inflammation and have depicted similar effectiveness as other NSAIDs [48]. Moreover it was found to be 3.7 and 6.5 times more potent inhibitor of COX-2 than diclofenac and amfenac [127]. The common adverse effect of bromfenac is hepatotoxicity [128-130] but 0.07 or 0.09% ophthalmic solution has shown no hepatotoxicity or other adverse effects [131-132]. No other formulation details of bromfenac is available for sustain release showing a large potential to explore such dimensions.

5.5. Diclofenac

Diclofenac, arylacetic acid derivative, is a nonselective inhibitor of COX. Generally it is dispensed as sodium, potassium and diethylamine salts. Commercially it is available as 0.1% solution (Voltaren® solution, Volta Oph® eye drops, Ophtha® eye drops, Flamar® eye drops) and indicated for the treatment of chronic conjunctivitis, keratoconjunctivitis, postoperative inflammation (in patients who have undergone cataract extraction). Moreover it is beneficial in temporary relief of pain and photophobia (in patients undergoing corneal refractive surgery),

painful post-traumatic condition of the cornea and conjunctiva. In physiologic pH of eye, diclofenac sodium is ionized, hence less permeated through cornea. At buffer solution of pH 6, the drug is less ionized and shows high drug permeability [133]. Further reduction of pH leads to less solubility of drug. Solubilizing agents such as polyoxyethylene-35-castor oil, hydroxypropyl-β-cyclo dextrin and n-octenylsuccinate have been added to improve solubility and permeation [134-135]. Diclofenac had also been formulated in oily vehicle and it was found that apparent corneal permeability coefficient of 0.2% diclofenac was maximum in sesame oil followed by safflower oil and castor oil [136]. To avoid precorneal loss, ocular liposomes of diclofenac sodium were investigated by Sun *et al.* (2006). Bioavailability of liposomes was found to be 211% greater than aqueous solution due to increased corneal residence time [137]. Diclofenac sodium 0.1% ophthalmic gels were formulated using 1% sodium carboxymethyl cellulose, 4% hydroxypropyl methylcellulose (HPMC) or 3% methylcellulose. The gel formulated using HPMC provided better ocular tolerance and sustained *in vitro* drug release up to 9 hour [138]. Diclofenac ocular insert using a combination of methylcellulose and sodium carboxymethyl cellulose depicted sustained release of diclofenac for 12 hour which can avoid multiple dosing [139]. Mucoadhesive thiolated ocular inserts comprising of polyacrylic acid-cysteine conjugate as polymeric matrix, containing either diclofenac sodium or diclofenac-tris(hydroxymethyl)-amino methane provided better retention [140]. Diclofenac ocular tolerability was improved with Sophisen (a novel carrier) when compared to aqueous solution [141].

5.6. Flurbiprofen

Flurbiprofen, a propionic acid derivative, is nonselective COX inhibitor. It is marketed in a concentration of 0.03% (Cadiflur® eye drop, Eyefen® eye drop, Flubichlor® eye drop and indicated for intraoperative miosis. The S-(+) isomer of flurbiprofen has been found to be 100 times more potent inhibitor of prostaglandin synthesis than the R-(−) isomer. The ideal pH for the delivery drug to the eyes is between 6 to 7 (recommended by USP, 2004). Allaire *et al.* (1994) had shown that there is no significant difference between 0.1% indomethacin and 0.03% flurbiprofen in maintaining preoperative mydriasis in cataract surgery regarding effectiveness and tolerance in a randomized double blind study [142]. Moreover these dosage of indomethacin and flurbiprofen was found to be more effective than 0.1% diclofenac [143]. Flurbiprofen is also found to be effective in post refractive surgery [144]. In order to improve bioavailability of drug various naparticulates systems has been developed. Flurbiprofen loaded poly(D,L-lactide-co-glycolide) nanospheres have shown two fold increase in penetration in *ex-vivo* studies [145]. Flurbiprofen loaded biodegradable poly(lactic/glycolic) acid nanoparticle showed high drug loading and better inflammation reducing ability in rabbit (sodium arachidonate induced inflammation) with no ocular toxicity [146].

5.7. Nepafenac

Nepafenac is an aryl acetic acid derivative and prodrug for enhanced corneal permeability. It crosses outer ocular barriers easily and its bioactivation is done by ocular tissues. Its activity was found to be much greater in iris, choroid and ciliary compared to cornea [147]. It has longer duration of action and can be valuable in postoperative ocular pain, inflammation, and posterior segment edema [148]. Clinically it is used as 0.1% ophthalmic suspension for postoperative cataract surgery (Nevanac® eye suspension) [149]. Nepafenac 0.1% ophthalmic suspension was found to be effective in preventing and treating ocular inflammation and pain associated with cataract surgery. During prolonged treatment, the metabolism of nepafenac appears to be sufficient to produce amfenac for treating inflammation and pain [150]. Walters *et al.* (2007) demonstrated high corneal bioavailability of nepafenac than amfenac, ketorolac, and bromfenac and it was significantly different than all three drugs. Moreover, nepafenac gets converted to amfenac in posterior ocular tissues that had shown greater potency of COX-2 inhibition than ketorolac and bromfenac [91]. Nepafenac had confirmed potentially effective in post refractive surgery compared to diclofenac [56].

5.8. Aceclofenac

Aceclofenac, an arylacetic acid derivative, is a non-selective inhibitor of COX but studies exhibited its higher selectivity for Cox-2 than Cox-1 [151]. ACE belongs to BCS Class II and possesses poor aqueous (60 μg/mL), which makes it an excellent candidate for ocular formulations [152]. An efficient permeation of aceclofenac was observed

through goat, sheep and buffalo cornea at physiological pH [153]. Mathurm et al developed glycero-gelatin ocular inserts (cross-linked) for improved bioavailability of aceclofenac. The cross-linked inserts exhibited sustained drug release and better pharmacodynamic activity when compared with non-cross-linked inserts [154]. Similarly, Dave at al successfully fabricated polymeric inserts with prolonged release of aceclofenac and minimum swelling within culdesac [155]. A significant anti-inflammatory activity of aceclofenac was noted from its topical gel formulation [156]. Katara et al. formulated a stable Polymer (Eudragit RL 100) based nanoparticulate system of aceclofenac for ocular delivery. The nanoformulation exhibited improved corneal permeation with no signs of corneal damage. The in vivo studies involving arachidonic acid-induced ocular inflammation in rabbits revealed significantly higher inhibition of by the nanoparticle formulation compared with the aqueous solution [157].

6. CONCLUSION

Inflammation is a non-specific immune response. It is the first defense mechanism of body against foreign substances but sometimes can lead to tissue damage, cardiovascular diseases and cancer. Eye inflammation is the one of major cause of blindness world over. NSAIDs are often used for such inflamed condition due to their improved safety profile. In broader way NSAIDs are classified as non-selective COX and preferential or selective COX-2 inhibitor, based on their mechanism of action. Preferential cyclooxygenase-2 inhibitors are preferred over non-selective COX inhibitors as constitutive cyclooxygenase-1 is obligatory for its physiological functions. During the course of time various NSAIDs have been evolved for topical ocular application as the topical route is preferred over systemic route for treating ocular manifestations. The development of a suitable ocular formulation containing NSAID is quite challenging as most of these have poor aqueous solubility. Researchers have used various Solubilization techniques, derivatives and oily vehicle to disperse such formulations. Bromfenac and nepafenac (metabolite COX-2 selective), COX-2 selective inhibitors are found to be promising for ocular inflammations. Approval of nepafenac and bromfenac by FDA has started a new phase for ocular topical delivery of preferential COX inhibitors. There is still a lot scope to further development of preferential COX inhibitors for topical ocular delivery.

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