2. REVIEW OF LITERATURE

Baeyens V. et al. 18 (1997) have optimized release of dexamethasone and gentamicin from a soluble ocular insert for the treatment of external ophthalmic infections. In the case of external ophthalmic infections, repeated instillations of antibiotics are required to reach therapeutic level, above the minimal inhibitory concentration (MIC). An additional administration of a corticosteroid is often needed, in order to limit the precorneal damages caused by the infection. However, repeated administration of a corticosteroid can increase intraocular pressure and thus lead to glaucoma. To overcome the disadvantages of separated and repeated instillations of two products and to avoid the side effects of dexamethasone, a soluble insert containing gentamicin sulfate and dexamethasone phosphate was developed. The new system ensures the concomitant release of the two drugs during the first 10 h of treatments, followed by an adequate concentration of gentamicin sulfate, above the MIC of 4.0 mcg ml⁻¹, during 50 h, due to a combination of gentamicin sulfate with cellulose acetate phthalate, which reduces the solubility of gentamicin.

Chetonia P. et al. 19 (1998) fabricated silicone rubber/hydrogel composite ophthalmic inserts. The present report describes the development and in vitro/in vivo testing of rod shaped mucoadhesive ophthalmic inserts fitting the upper or lower conjunctival fornix. Cylindrical devices (diameter 0.9 mm, length 6–12 mm, weight 3–8 mg) all containing 0.8 mg oxytetracycline HCl (OXT) were prepared from appropriate mixtures of silicone elastomer, OXT and sodium chloride as release modifier. A stable polyacrylic acid (PAA) or polymethacrylic acid (PMA) interpenetrating polymer network (IPN; 30 or 46% w/w) was grafted onto the inserts’ surface by treatment with a mixture of acrylic (or methacrylic) acid and ethylene glycol dimethacrylate in xylene at 100°C. The inserts were tested for drug release in vitro and for drug release and retention in rabbit eyes. The presence of IPN, as well as NaCl, in general increased the drug release rate. The PMA-grafted devices released OXT at lower rates when compared with the PAA-grafted ones. A nearly zero order release rate for about 1 week was observed in vitro for some types of inserts. The ocular retention of IPN-grafted samples was significantly higher with respect to ungrafted ones. The presently described mucoadhesive silicone inserts might prove efficient therapeutic systems for chemotherapy of ocular bacterial infections, such as trachoma.
Manvi FV. et al.\textsuperscript{20} (1997) developed timolol maleate circular ophthalmic inserts by solvent casting using cellulose acetate as polymer with PEG 600 and diethyl phthalate (DEP) as plasticizers in two different concentrations. Plasticizer system influences their effect on drug release. The correlation was obtained in both \textit{in vivo} and \textit{in vitro} methods.

Narasimha Murthy S. et al.\textsuperscript{21} (1997) described the preparation and \textit{in vitro} – \textit{in vivo} evaluation of polymeric ophthalmic inserts containing diclofenac sodium with biodegradable polymer, E-caprolactone. The medicated discs were evaluated for their uniformity, \textit{in vitro} drug release, ocular toxicity and stability. The sterilized formulations were subjected for \textit{in vivo} drug release studies. The films showed good physical features and stability. Ophthalmic inserts were proved nontoxic and resulted in appreciable bioavailability.

Vijaya MM. et al.\textsuperscript{22} (1998) have prepared ophthalmic inserts of diclofenac sodium by solvent casting method. Diclofenac sodium ophthalmic inserts were prepared using different polymers such as hydroxylpropyl methylcellulose (HPMC), methylcellulose (MC) and polyvinyl pyrrolidone (PVP) in various proportions. \textit{In vitro} diffusion studies, evaluation studies and infrared spectra (I.R.) studies were conducted. Results showed that formulation of diclofenac sodium has achieved the objectives of increased contact time, prolonged release, decrease frequency of administration and thus may improve the patient compliance.

Saisivam. S. et al.\textsuperscript{23} (1999) evaluated ciprofloxacin hydrochloride ocuserts using different polymers in various proportions and combinations. The \textit{in vitro} release of drug from the formulations was studied using a commercial semipermeable membrane. The physicochemical parameters of the ocuserts were evaluated. A zero order release from formulation VI (Drug reservoir with 2\% HPMC and 6\% EC as rate controlling membrane) was subjected to \textit{in vivo} studies using rabbits. The result indicated a good correlation between \textit{in vitro} and \textit{in vivo} studies. The expected release for an extended period of 24\,h was observed in formulation VI.

Lee YC. et al.\textsuperscript{24} (1999) have studied the formulation and \textit{in vivo} evaluation of ocular insert containing phenylephrine and tropicamide A Gelfoam\textsuperscript{®} based ocular device containing 1.7 mg of phenylephrine and 0.6 mg of tropicamide was formulated and evaluated for pupillary dilation in rabbits. The manufacturing procedure was fairly simple and the required excipients were inexpensive. The \textit{in vivo} results show that the mydriatic response produced
by the proposed device was larger and longer lasting than that produced by eye drops with an equivalent amount of phenylephrine and tropicamide. The results reported in this study, along with those of previous studies, imply that Gelfoam® was a versatile drug carrier for either local or systemic drug delivery via the ophthalmic route.

Colo GD. et al.25 (2001) have prepared the gel forming erodible inserts for ocular controlled delivery of ofloxacin. Inserts of 6 mm diameter, 20 mg weight, medicated with 0.3 mg ofloxacin, were prepared by powder compression. The in vitro drug release from inserts was mainly controlled by insert erosion. The erosion time scale was varied by compounding polyethylene oxide (PEO) with eudragit L100 (EUD) 17% neutralized (EUDNa17) or 71% neutralized (EUDNa71). The insert erosion rate depended on the strength of interpolymer interactions in the compounds and on the hydrophilichydrophobic balance of compounds. Immediately after application in the lower conjunctival sac of the rabbit eyes, the inserts based on plain PEO, PEO–EUDNa17 or PEO–EUDNa71 formed mucoadhesive gels, well tolerated by the animals; then the gels spread over the corneal surface and eroded. Compared to commercial ofloxacin eye drops, drug absorption into the aqueous humor was retarded by the PEO–EUDNa71 inserts, and both retarded and prolonged by the PEO–EUDNa17 inserts. Bioavailability increase has been described to PEO mucoadhesion and increased tear fluid viscosity.

Karatas A. et al.26 (2001) studied indomethacin inserts prepared by water soluble polymers. Inserts containing indomethacin were prepared using water soluble polymers such as hydroxypropyl cellulose, methylcellulose, hydroxypropyl methylcellulose and polyvinyl alcohol by the film casting method. In this study, they examined the relation between swelling behavior of the polymer and the release of the indomethacin from inserts. Thus an electric device for measuring the thickness of the hydrated inserts was developed. The results were interpreted from normalized increase in thickness of the hydrated inserts. The mechanism of drug release was identified by means of the value of the ratio R/F (Relaxational to fickian contribution ratio), calculated according to the equation developed by Peppas. When the ratio R/F of the inserts decreased, drug release from the inserts became diffusive. As the normalized thickness of the inserts increased, the rate of drug release decreased.
Gerald Rajan NSM et al. (2001) investigated controlled release of tetracycline HCl from ophthalmic inserts with the aim of achieving once a day administration. Drug reservoir and rate controlling membrane were prepared using different hydrophilic polymers such as HPMC, MC, PVP (K-30) and hydrophobic ethyl cellulose respectively. The ocular inserts were evaluated for their physico chemical properties, in vitro kinetics and in vivo release characteristics. They concluded that the targeted zero order mode of release was observed in formulation F6 (Drug reservoir with 2% HPMC and 4% EC as rate controlling membrane), its in vivo release characteristics were evaluated using rabbits as animal models. The in vitro release kinetics data was treated according to diffusion models proposed by Higuchi and Peppas in order to access the mechanism of drug release.

Kawakami S. et al. (2001) studied the controlled release and ocular absorption of tilisolol utilizing ophthalmic insert incorporated lipophilic prodrugs. To control ocular drug delivery, the O-butryl ester prodrug of tilisolol (BUTL) and the O-palmitoyl ester prodrug of tilisolol (PalTL) were incorporated into an ophthalmic insert. The released TL from BUTL inserts and PalTL inserts in pH 7.4 phosphate buffered saline until 5 h were 25% and 3% of that from TL inserts, respectively. In addition, BUTL was also released from BUTL inserts. However, PalTL was not released from the PalTL insert. The release of drugs from TL inserts and BUTL inserts was little affected by the addition of bovine serum albumin (BSA) in pH 7.4 phosphate buffered saline. In contrast, the release of drugs from PalTL inserts was enhanced by the addition of BSA. After application of TL, BUTL, and PalTL inserts to the rabbit eye, the aqueous humor concentration of TL was prolonged compared with TL instillation and the plasma concentration of TL was much lower than that of TL instillation. The ratios of the area under the TL concentration time- curve, AUC in the aqueous humor to AUC in the plasma (AUCaqueous /AUCplasma ) after application of aqueous plasma BUTL until 8 h were 3.1 fold and 3.8 fold higher than those of the TL insert and PalTL insert, respectively.

Dhanaraju MD. et al. (2002) developed bioadhesive ocuserts matrix for ophthalmic administration of ciprofloxacin hydrochloride. The bioavailability of ciprofloxacin hydrochloride to the ophthalmic epithelium is very low and when the drug is administered in the form of ophthalmic ointment, dose should be applied for every four h. In order to increase the ocular bioavailability, ciprofloxacin hydrochloride ocuserts have been developed with the aim of promoting the prolonged release of the drug using polyvinyl alcohol. Ocular drug delivery polymer matrix discs were evaluated for the uniformity of drug content, in vitro drug
release, toxicity and stability. The sterilized formulations were subjected for *in vivo* drug release studies. These films showed good physical features and stability. They were proved nontoxic and resulted in appreciable bioavailability.

**Pandit JK. et al.** *(2003)* studied the effect of physical cross linking on *in vitro* and *ex vivo* permeation of indomethacin from polyvinyl alcohol ocular inserts. Polymeric ophthalmic inserts containing indomethacin were formulated with combination of two different types of polyvinyl alcohol (high and low molecular weight) and physically reinforced by heating (80° and 100° C for 24 and 48 h) and freeze thawing (3 and 6 cycles). *In vitro* drug release and permeation genetic across goat cornea was studied in a continuous flow through apparatus and a modified keshary-chien cell respectively and compared with the non-reinforced inserts. They concluded that the rate of indomethacin release was inversely proportional to low molecular weight polyvinyl alcohol content. The duration of heating had more effect on drug release than the temperature and freeze thawing was more successful in retarding the drug release. The permeation of indomethacin correlated well with the *in vitro* release.

**Dandagi PM. et al.** *(2003)* prepared ketorolac tromethamine ocular films. Kotorolac tromethamine ocular films were formulated using polyvinyl alcohol, polyvinyl pyrrolidone and sodium CMC polymeric combination by solvent casting techniques. Glycerin and PEG 400 were used as plasticizer. From the result obtained it can be concluded that as the proportion of polyvinyl pyrrolidone increases in the film, the drug release rate increases and decreases with increasing proportion of polyvinyl alcohol. Prepared ocular films showed good *in vitro, in vivo* correlation, which indicate that the *in vitro* method adopted simulated the eye condition. To establish more precise *in vivo* release pattern it is obligatory to reduce possible variables by performing the study in large number of replicates.

**Sasaki H. et al.** *(2003)* fabricated one-side-coated insert as a unique ophthalmic drug delivery system. Unique one-side-coated insert that releases drug from only uncoated side. The purpose of this study was to determine whether ocular and systemic absorption of ophthalmic drug could be altered by an inserting direction of the insert in rabbit eyes. One-side-coated insert was prepared by attaching a polypropylene tape on the one side of the polymer disc of poly (2-hydroxypropyl methacrylate) (HPM) containing tilisolol as a model ophthalmic drug. The insert was applied in the lower conjunctival cul-de-sac of albino rabbits with the uncoated side facing bulbar conjunctiva/sclera (SC insert) or palpebral conjunctiva
(CJ insert). At the adequate intervals, the tear fluid, plasma, aqueous humor, conjunctiva and sclera were collected and the drug concentrations were determined by an HPLC. A release of tilisolol from the one-side-coated insert was twice slower than from the uncoated insert. Ocular application of the one-side-coated insert produced the constant concentrations of tilisolol in the tear fluid over 180 min. SC insert showed higher drug concentrations in the aqueous humor and sclera and lower drug concentrations in the plasma and conjunctiva than CJ insert.

**Margit H. et al.** (2003) investigated mucoadhesive ocular insert based on thiolated poly (acrylic acid). The aim of the study was to develop a mucoadhesive ocular insert for the controlled delivery of ophthalmic drugs and to evaluate its efficacy in vivo. Water uptake and swelling behavior of the inserts as well as the drug release rates of the model drugs fluorescein and two diclofenac salts with different solubility properties were evaluated in vitro. Fluorescein was used as fluorescent tracer to study the drug release from the insert in humans. Inserts based on thiolated poly (acrylic acid) were not soluble and had good cohesive properties. A controlled release was achieved for the incorporated model drugs. The in vivo study showed that inserts based on thiolated poly (acrylic acid) provide a fluorescein concentration on the eye surface for more than 8 h, whereas the fluorescein concentration rapidly decreased after application of aqueous eye drops or inserts based on unmodified poly (acrylic acid). The present study indicates that ocular inserts based on thiolated poly (acrylic acid) are promising new solid devices for ocular drug delivery.

**Charoo NA. et al.** (2003) reported ophthalmic delivery of ciprofloxacin hydrochloride from different polymeric formulations. Reservoir type ocular inserts were fabricated using sodium alginate containing ciprofloxacin hydrochloride as the core (drug reservoir) that was sandwiched between the Eudragit and/or polyvinyl acetate films. Ocular inserts were packaged in aluminum foil and sterilized by γ radiation. These were tested for sterility as per British Pharmacopoeia (BP). Ocular inserts were evaluated for in vitro release rate studies, microbial efficacy, in vivo release studies, efficacy against induced bacterial conjunctivitis in rabbit’s eyes, concentration in the aqueous humor, and stability studies as per the International Conference on Harmonization (ICH) guidelines. Ocular inserts passed the test for sterility. They showed zero order release of the drug in the in vitro and in vivo release studies over a period of 120 h. The drug was found to be active against selected microorganisms as was proved by microbial efficacy studies. A high correlation coefficient
was found between in vitro and in vivo release rate studies. Better improvement was observed in artificially induced bacterial conjunctivitis in rabbit's eyes, compared with marketed eye drops and placebo. Drug concentration in the aqueous humor was found above Minimum Inhibitory Concentration (MIC-90) against selected microorganisms. Shelf life of the product was found to be more than 2 years.

Rao V. et al.\textsuperscript{35} (2004) have developed ocular inserts containing norfloxacin. Norfloxacin is a poorly water soluble drug and to improve its solubility it was complexed with b-cyclodextrin (BCD). Several ocular patches/inserts of norfloxacin-b-cyclodextrin were prepared in hydroxypropyl methylcellulose (HPMC) matrix. The influence of rate controlling membranes made of ethyl cellulose (EC) alone and in combination with polyvinyl pyrrolidone K30 (PVP K30) in different proportions on drug release kinetics was studied. The data were subjected to regression analysis. Various physical characteristics of the films were evaluated. In vitro release studies were carried out in a fabricated flow through cell. All the films prepared were found to be uniform in thickness and the partition coefficient of norfloxacin and its betacyclodextrin complex was 0.048 and 0.853 respectively. I.R. spectra revealed complexation of norfloxacin with b-cyclodextrin. In vitro results revealed that patch/insert formulations, V1 and V2, followed perfect zero order kinetics release (n = 1), and 3 formulations, V3, V4 and V5, released the drug by super case II kinetics (n > 1). The study confirmed the improved solubility of norfloxacin when complexed with b-cyclodextrin and that it can be delivered through films made of HPMC matrix cast with EC alone or with combination of PVP. It was also observed that increasing the proportion of PVP K30 into EC increased the rate of release of norfloxacin.

Harishkumar SL. Et al.\textsuperscript{36} (2004) studied in vitro characterization of physically reinforced ocular inserts of indomethacin. Physical reinforcements of polyvinyl alcohol based ocular inserts of indomethacin were conducted by subjecting to heat (80° C and 100° C for 24 and 48 h) and freeze thaw cycles (3 and 6 cycles). In vitro drug release was studied in a continuous flow- trough apparatus and compared with the non-reinforced inserts. The rate of indomethacin release was inversely proportional to the content of low molecular weight PVA (PVA, 14,000). The duration of heating had more effect on release properties than the temperature and the release pattern of freeze thawed inserts showed lower drug release than the non-reinforced and heat treated inserts.
Mundada AS. et al. (2006) developed soluble ocular inserts of ciprofloxacin hydrochloride with the aim of achieving once a day administration. Drug reservoir was prepared using natural hydrophilic polymer viz. gelatin while rate-controlling membrane was prepared using hydrophobic ethyl cellulose. Ocular inserts were evaluated for their physicochemical parameters like thickness, weight uniformity, drug content, percent moisture loss, and percent moisture absorption. The in vitro drug release studies were carried out using Bi-chambered donor receiver compartment model. Since targeted prolong release was observed in formulation CF2 and CF5, these formulations were further subjected to in vivo drug release study using rabbits as an animal model. In vitro drug release kinetic data was treated according to zero, first, and Higuchi kinetics to access the mechanism of drug release. Correlation between in vitro and in vivo drug release was found to be strong revealing the efficacy of the formulation. Formulation CF5 has achieved target of present study such as increase residence time, prolong drug release, reduction in frequency of administration and thus may improve the patient compliance.

Sreeniivas SA. et al. (2006) have developed ocular inserts with prolonged release of drug and minimum swelling within cul-de-sac using ofloxacin as a model drug and hydroxypropyl methyl cellulose, methyl cellulose, poly vinyl pyrrolidone and poly vinyl alcohol as polymers. PEG-400 was incorporated as plasticizer. The main purpose of the study was to deliver the drug in zero order kinetics. Solvent casting technique was followed to prepare ofloxacin ocular films. Eight formulations were formulated and subjected to various physicochemical evaluations. Ocular inserts prepared were smooth and passed all the evaluation tests performed. Formulation OF2 showed a maximum cumulative percentage drug release of 91.27 % at the end of 24 h. Ocuserts formulated also passed the test for sterility. They showed zero-order release of the drug in the in vitro and in vivo release studies. The drug in the films was found to be active against selected microorganisms as was proved by microbial efficacy studies. A high correlation coefficient was found between in vitro and in vivo release rate studies. Shelf life of the product was found to be more than one year. The results of in vitro, in vivo, kinetic treatment (zero order and Krosemeyer regression values) and rate constant ‘k’ value suggest that OF2 was the best formulation among the formulations studied for formulating ofloxacin ocular insert.

Sankar V. et al. (2006) have studied the design and evaluation of diclofenac sodium ophthalmic inserts. Diclofenac sodium ophthalmic inserts were prepared by using methyl
cellulose (MC), sodium carboxymethyl cellulose (SCMC) alone and in combination. Weight variation, thickness, drug content, ocular irritation and stability of medicated inserts were evaluated. *In vitro* study was carried out by using a semipermeable dialysis membrane. According to the results, 97% of drug was released from the formulation containing 4% SCMC and 1% MC in combination over a period of 12 h. Release followed zero order kinetics. Medicated inserts were subjected to UV irradiation and *in vivo* drug release studies. No significant change was observed in the drug content and physical features during storage at 30°C and 40°C for 2 months. From this study it was concluded that ophthalmic inserts prepared with 4% SCMC and 1% MC in combination showed sustained release and were found to be stable.

**Kamel AE. et al.** (2010) reported environmentally responsive ophthalmic gel formulation of carteolol hydrochloride. Environmentally responsive gel formulation for ocular controlled delivery of carteolol hydrochloride was developed in an attempt to improve ocular bioavailability and hence decrease its systemic absorption and side effects. The viscosity and the ability of the prepared formulations to deliver carteolol hydrochloride *in vitro* and *in vivo* were monitored and compared with an aqueous commercial solution. The effect of polymer concentration and drug concentration on the *in vitro* release of carteolol hydrochloride was examined. Gelrite formulations showed pseudoplastic behavior with thixotropic characteristics and the viscosity of the prepared systems increased as the concentration of the polymer increased. At fixed drug concentrations, as the Gelrite concentration increased, the drug release decreased. At fixed polymer concentrations, as the drug concentration increased the release of drug increased. Gelrite formulation (0.4% w/w) containing 1% drug showed significantly improved bioavailability compared with the commercial aqueous solution (Arteoptic® 1%). The developed *in situ* gel formulation showed potential for use as delivery systems with superior ocular bioavailability of carteolol hydrochloride.

**Balasubramaniam J. et al.** (2009) studied *in vitro* evaluation of polyvinyl alcohol based ocular inserts of ciprofloxacin hydrochloride. Soluble inserts of ciprofloxacin hydrochloride using high and low molecular weight polyvinyl alcohol alone and in various combinations were prepared by a casting technique. The *in vitro* drug release from the prepared inserts was studied using a continuous flow through model, developed in laboratory. The antimicrobial efficacies of the prepared inserts against common ocular pathogens. viz., staphylococcus
aureus and pseudomonas aeruginosa were evaluated using a modified *in vitro* microbiological model. Ciprofloxacin hydrochloride release from the inserts followed matrix diffusion kinetics showing an anomalous release mechanism based on the calculated release exponent (n) value. Drug release increased with an increase in proportion of high molecular weight polyvinyl alcohol in the inserts. The *in vitro* microbiological model demonstrated the effectiveness of the inserts against the two microorganisms. The result of the *in vitro* release studies correlated well with that of the antimicrobial studies.

Jayprakash S. et al.\textsuperscript{42} (2011) have developed gentamicin sulphate ocuserts. Gantamicin sulphate ocuserts were prepared using different polymer such as hydroxylpropyl methylcellulose (HPMC), methylcellulose (MC), polyvinyl pyrrolidone (PVP), ethyl cellulose (EC) and microcrystalline cellulose (MCC), at different concentration and combinations. The ocuserts were prepared by using solvent casting technique. The prepared ocuserts were evaluated for moisture absorption, moisture loss, thickness, weight variation and drug content. The *in vitro* release of drug from the formulations was studied using commercial semi permeable membrane. A zero order release formulation F6 was sterilized by ethylene oxide and subjected to *in vivo* studies. IR spectral observations showed no interaction with polymer indicates the intactness of the drug in formulation.