3. REVIEW
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3.1 OCULAR DRUG DELIVERY SYSTEMS

Baeyens V. et al.\textsuperscript{41} have optimized release of dexamethasone and gentamicin from a soluble ocular insert for the treatment of external opthalmic infections. In the case of external opthalmic 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\textsuperscript{-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.\textsuperscript{42} fabricated silicone rubber/hydrogel composite opthalmic inserts. The present report describes the development and \textit{in vitro/in vivo} testing of rod shaped mucoadhesive opthalmic 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 \textit{in vitro} and for drug release and retention in rabbit eyes. The presence of IPN, as well as of 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 \textit{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{43} 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{44} 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{45} 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{46} 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.\(^{47}\) have studied the formulation and *in vivo* evaluation of ocular insert containing phenylephrine and tropicamide. A Gelfoam® 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 *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.\(^{48}\) 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 of 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 poly ethylene 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 hydrophilic-hydrophobic 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.\(^{49}\) 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.** 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.** studied the controlled release and ocular absorption of tilisolol utilizing ophthalmic insert incorporated lipophilic prodrugs. To control ocular drug delivery, the O-butyryl 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 (AUC<sub>aqueous</sub> /AUC<sub>plasma</sub> ) after application of aqueous plasma BUTL
Dhanaraju MD. et al.\textsuperscript{52} developed bioadhesive ocu-serts 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 ocu-serts 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, \textit{in vitro} drug release, toxicity and stability. The sterilized formulations were subjected for \textit{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.\textsuperscript{53} studied the effect of physical cross linking on \textit{in vitro} and \textit{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). \textit{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 \textit{in vitro} release.

Dandagi PM. et al.\textsuperscript{54} prepared ketorolac tromethamine ocular films. Ketorolac 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 \textit{in vitro}, \textit{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.*\(^5^5\) 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.*\(^5^6\) 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.\textsuperscript{57} 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 \textit{in vitro} release rate studies, microbial efficacy, \textit{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 \textit{in vitro} and \textit{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 \textit{in vitro} and \textit{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{58} 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. \textit{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 betacycldextrin complex was 0.048 and 0.853 respectively. I.R. spectra revealed complexation of norfloxacin with b-cyclodextrin. \textit{In vitro} results revealed that patch/insert formulations, V1 and
Harishkumar SL. et al.\textsuperscript{59} studied \textit{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$^\circ$ C and 100$^\circ$ C for 24 and 48 h) and freeze thaw cycles (3 and 6 cycles). \textit{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.\textsuperscript{60} 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 \textit{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 \textit{in vivo} drug release study using rabbits as an animal model. \textit{In vitro} drug release kinetic data was treated according to zero, first, and Higuchi kinetics to access the mechanism of drug release. Correlation between \textit{in vitro} and \textit{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.\textsuperscript{61} 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 \textit{in vitro} and \textit{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 \textit{in vitro} and \textit{in vivo} release rate studies. Shelf life of the product was found to be more than one year. The results of \textit{in vitro}, \textit{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.

\textbf{Sankar V. et al.} 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. \textit{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 \textit{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.

\textbf{Kamel AE. et al.} 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.

Sultana Y. et al.3 developed ocular inserts for controlled delivery of pefloxacin mesylate. Reservoir type ocular inserts were prepared by the film casting technique in teflon coated petridish and characterized in vitro by drug release studies using flow through apparatus that simulated the eye conditions. Six formulations were developed, which differed in the ratio of polymers eudragit RS 100 and eudragit RL 100 used for the preparation of the rate controlling membrane. All formulations carried 0.72 mg pefloxacin mesylate, 2.69 mg polyvinyl pyrrolidone (PVP) K-30, plasticizers, propylene glycol (10%m/m) and dibutyl phthalate (15% m/m). The optimized formulation was subjected to microbiology studies, in vivo studies, interaction studies and stability studies to assess the effectiveness of the formulation. Cumulative drug released from the formulation ranged from 90-98% within 48 to 120 h. On the basis of in vitro drug release studies, the formulation with Eudragit RS 100/Eudragit RL 100 (4:1) was found to be better than the other formulations and it was selected as an optimized formulation. On the basis of in vitro, microbiological studies, in vivo drug release, interaction and stability studies, they can concluded that this ocular inserts formulation provided the desired drug release in vitro for 5 days and remained stable and intact at ambient condition.

Balasubramaniam J. et al.64 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.\(^6^5\) have developed gentamicin sulphate ocuserts. Gantamicin sulphate ocuserts were prepared using different polymer such as hydroxypropyl 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.

Mukherjee P. et al.\(^6^6\) formulated sulphacetamide sodium ocular inserts. Ocular inserts were prepared using sulphacetamide sodium as a model drug and hydroxypropyl methylcellulose, methylcellulose, polyvinyl pyrrolidone alcohol as polymers. PEG-400 and glycerine were incorporated as plasticizers. Eight formulations were formulated and subjected to various physicochemical evaluations. Ocular inserts passed the test for sterility. They showed zero order release of drug in the *in vitro* and *in vivo* release studies.

Vijayendra SM. et al.\(^6^7\) formulated sustained drug delivery system for betaxolol. Five batches of matrix type ocular films of betaxolol containing 1.0, 1.5, 2.0, 2.5 and
3.0% w/v of sodium alginate prepared by molding technique and evaluated for their average weight and weight variation, thickness, drug content, *in vitro* drug release, sterility and aging studies. An increase in average weight and thickness is due to increase in polymer concentration. A batch prepared with 3.0% w/v of sodium alginate exhibited maximum average weight of 9.07 mg/cm² and thickness of 188 µm respectively. The drug content was ranging from 0.492-0.501 mg/cm². The *in vitro* drug release studies showed that increase in polymer content decrease the drug release from ocular inserts. Batches prepared using 1.5% w/v sodium alginate showed sustained and almost complete release (98.89%) over 6 h period was selected as an ideal batch. Sterility testing for an ideal batch was conducted in two different culture medium and also its aging at room temperature for a period of 2 months was investigated. It was concluded that the ocular films of betaxolol is capable of exhibiting sustained drug release with an ideal sterility and aging profile.

Ahuja M. *et al.* evaluated gellan based ocular inserts of phenylephrine. Gellan gum based ocular inserts of phenylephrine were prepared by solvent casting method and evaluated for uniformity of thickness, weight, drug content, surface pH, *in vitro* release and *in vivo* mydriatic response in rabbits. The inserts were found to release drug following Higuchi square root release kinetics. *In vivo* comparison of the inserts with three times dosing of the conventional eye drop formulation revealed a comparable intensity and extent of mydriatic response produced by inserts. It can be concluded from the study that gellan gum based ocular inserts of phenylephrine can be effectively used for sustained topical ocular delivery.

Liu Z. *et al.* studied the ocular pharmacokinetics of ion-activated *in situ* gelling ophthalmic delivery system for gatifloxacin by microdialysis. The poor bioavailability and therapeutic response exhibited by conventional ophthalmic solutions due to rapid precorneal elimination of the drug may be overcome by the use of gel system. The present work was conducted to evaluate the relative bioavailability of ion-activated in situ ophthalmic gel of gatifloxacin by microdialysis. The conventional ophthalmic solution of gatifloxacin was used as reference. The AUC of test group is 3.8-fold vs. the reference group (1.4316 ± 0.1327 µg·mL⁻¹·h vs. 0.3756 ± 0.0380 µg·mL⁻¹·hr) (*P* < 0.05), and the Cₘₐₓ of test group vs. the control group is 3.0-fold (0.3363 ± 0.0634 µg·mL⁻¹ vs. 0.1112 ± 0.0151 µg·mL⁻¹) (*P* < 0.05). The Tₘₐₓ of test group is longer than
that of reference group (2.0 ± 0.67 h vs. 0.667 ± 0.17 h) ($P < 0.1$) and $K_e$ of test group is lower than that of reference group. The developed formulation has a higher bioavailability and longer residence time in aqueous humor than conventional ophthalmic solutions. The developed system is a viable alternative to conventional eye drops.

Budai L. et al.\textsuperscript{70} developed ciprofloxacin containing therapeutic systems using gel and liposome based formulations to minimize tear driven dilution in the conjunctival sac, a long-pursued objective in ophthalmology. Physicochemical properties (pH, osmolarity, viscosity, expansivity, membrane fluidity and \textit{in vitro} ciprofloxacin release rate) of the preparations were studied by the appropriate methods. For gel preparation, the bioadhesive poly (vinyl alcohol) and polymethacrylic acid derivatives were applied in various concentrations. Liposome-supported carrier systems, multilamellar vesicles from lecithin and 1-dipalmithoyl-phosphatidylcholine provided the encapsulating agent. Electron paramagnetic resonance (EPR) spectroscopy was applied to study the molecular interactions in the ophthalmic formulations. The polymer hydrogels used in the preparations ensured a steady and prolonged active ingredient release. In addition, encapsulation of the ciprofloxacin into liposomes prolonged the \textit{in vitro} release of the antibacterial agent depending on the lipid composition of the vesicles.

Patel D. et al.\textsuperscript{71} developed polymeric ocular drug delivery system for controlled release of ofloxacin. Ocular films of ofloxacin were prepared with the objectives of reducing the frequency of administration to improve patient compliance, obtaining controlled release and greater therapeutic efficacy in the treatment of eye infections such as blepharoconjunctivitis, keratoconjunctivitis, keratitis, corneal ulcers etc. HPMC-ofloxacin matrices were prepared by mercury substrate method. The influence of rate controlling membrane of different polymers (ethyl cellulose, eudragit RL 100 and RS 100) on release kinetics was studied. These ocular films were evaluated for physicochemical characteristics. The prepared films were found to be flexible and transparent. The average weight and thickness of were found to be 6.4-11.3 mg and 48.4-87.5 microns respectively. The drug content varied from 99.2-104.6%. The exposure to UV radiations sterilized the ocular films and no microbial growth was observed in any formulation in sterility testing by direct inoculation method. The
formulations were subjected to \textit{in vitro} and \textit{in vivo} release studies. OF-3 with rate controlling membrane of eudragit RS 100 followed perfect zero order release kinetics. \textit{In vivo} studies carried out in the eyes of rabbits showed controlled release upto 24 h. There was a good correlation between the \textit{in vitro} and \textit{in vivo} data.

\textbf{Mundada AS. et al.}\textsuperscript{72} had formulated soluble ocular inserts of ciprofloxacin hydrochloride to increase residence time and prolong drug release. Drug matrices were prepared using natural polymer. Gelatin, a biodegradable polymer, was tried for the first time in the preparation of soluble ocular drug insert matrices. The inserts were then evaluated for their physicochemical parameters. The \textit{in vitro} drug release studies were carried out using a bi-chambered donor receiver compartment model. \textit{In vivo} drug release was carried out using rabbits as animal models. Formulations CF4 and CF8, which showed controlled and prolonged \textit{in vitro} drug release, were subjected to \textit{in vivo} study. \textit{In vitro} and \textit{in vivo} correlation was found to be strong, revealing the efficacy of the formulation. Formulation CF8 was found promising, as it achieved the target of the present study.

\textbf{Khan S. et al.}\textsuperscript{73} developed reservoir type ocular inserts comprising reservoir film of sodium alginate and rate controlling membrane consisting of different eudragit RL 100: RS 100 ratios were prepared by film casting technique on teflon coated petri dishes and tested for drug content, physical characteristics, interaction between drug and polymers due to sterilization by $\gamma$ radiations and \textit{in vitro} drug release. Reservoir film containing 2.5\% sodium alginate and 48\% PEG 400 by weight of polymer as plasticizer was considered best for formulation of ocular insert owing to maximum percentage elongation at break (18 $\pm$ 0.57). Based on \textit{in vitro} drug release studies formulation containing 3.5:1.5 of Eudragit RL 100/RS 100 (D4) was found better than other formulations with 98\% drug release in 120 h therefore, selected as optimized and subjected to \textit{in vivo} and stability studies. High \textit{in vitro}–\textit{in vivo} release correlation (0.977) was observed for the formulation. Concentration of acyclovir in aqueous humor reached above the reported minimum effective concentration of 1.7 $\mu$g/ml after 8 h and remained almost constant up to 5 days however, acyclovir concentration could not be detected after 4 h on administration of 3\% ophthalmic ointment. Ocular inserts were stable with no sign of interaction due to $\gamma$ radiation and demonstrated controlled release of acyclovir for 5 days. Thus \textit{in vivo} studies conclusively demonstrates
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capability of ocular insert consisting rate controlling membrane of Eudragit RS 100 and eudragit RL 100 in controlling release of acyclovir to the eye. Therefore, administration of the ocular insert with an immediate release ointment would probably offset the initial lag time and maintain almost constant concentration in aqueous humor.

Mishra DN. et al.\textsuperscript{74} have prepared gel-forming ocular films of gatifloxacin sesquihydrate with different concentration of sodium alginate and chitosan. The surface of film was treated with 0.2 M calcium chloride solution. Various parameters of formulations including physicochemical properties and bioadhesion were evaluated. Drug release from the prepared films was evaluated using a donor receptor compartment model. The formulation F5 (2% sodium alginate and 1% chitosan) showed most prolonged drug release of 24 h indicating the potential of surface cross linking of the film to sustain the drug release. The gelation and residence time studies were carried out for the optimized formulation F5. The \textit{in vivo} drug release was also studied and correlated with \textit{in vitro} release pattern. \textit{In vivo} drug release and \textit{in vitro} antimicrobial studies carried out for the formulation F5 indicates the superiority of the ocular films over the marketed eye drop. These results demonstrate that the surface treated alginate-chitosan film could be potential vehicle to enhance ocular GS bioavailability and patient compliance.

Wagh VD. et al.\textsuperscript{75} have studied the formulation and evaluation of ophthalmic insert drug delivery system of forskolin. Forskolin, a diterpene obtained from natural roots of \textit{Coleus forskohlii} (wild) Briq. (Family: \textit{Lamiaceae}), reduces intraocular pressure (IOP) by 23-28\%, which is a desirable feature for an antiglaucoma therapy. Polyvinyl alcohol-14000 based ophthalmic inserts of pure forskolin (PVA-OIF) were prepared as matrix drug delivery with the aim of achieving once a day administration. Ophthalmic inserts were prepared using polymer PVA in various concentrations. The ophthalmic inserts were evaluated for evaluation parameters and \textit{in vitro} drug release. The \textit{in vitro} release data was treated according to diffusion model proposed by Higuchi and Peppas in order to access the mechanism of drug release. The batch formulated with PVA-14000 (1.5\%), showed sustained drug release behavior over a period of 6 h.
Patel UL. et al.\textsuperscript{76} formulated the indomethacin ophthalmic inserts. Indomethacin, a non-steroidal anti-inflammatory drug, has a pronounced analgesic antipyretic and anti-inflammatory action. The prostaglandin inhibitory action of indomethacin has been shown to be useful in relief of pain, muscular edema and other ocular inflammatory condition. An attempt has been made to formulate indomethacin ophthalmic inserts using hydroxy propyl methylcellulose, methylcellulose and gelatin as polymers by solvent casting method with aim of increasing the contact time, achieving controlled release, reduction in frequency of administration, improving patient compliance and greater therapeutic efficacy. The prepared ophthalmic inserts were then evaluated for uniformity of thickness, weight, drug content and swelling index. In vitro drug release studies of formulated ocuserts were performed by studying the diffusion through artificial membrane (prehydrated cellophane). IR spectral studies were performed to confirm the interaction of drug in formulation using KBr disc method. Out of twelve formulations prepared, the formulation containing indomethacin and HPMC (1:2) showed complete and prolonged release with 97.92% at the end of 7 h. The in vitro release kinetic data was treated according to diffusion model proposed by Higuchi and Peppas in order to access the mechanism of drug release.

3.2 DRUG PROFILE

3.2.1 Gatifloxacin sesquihydrate

Structural formula

![Structural formula of Gatifloxacin sesquihydrate](image)

\textbf{Molecular formula} \quad : \text{C}_{19}\text{H}_{22}\text{FN}_{3}\text{O}_{4.1/2}\text{H}_{2}\text{O}

\textbf{Category} \quad : \text{Flouroquinolone antibiotic}
Chemical name: 1 cyclopropyl-6-fluoro-1, 4-dihydro-8 methoxy-7-(3-methyl-1-piperazinyl)- 4 oxo-quinoline carboxylic acid sesquihydrate

Molecular weight: 375.40

Description: White to off-white powder.

Melting point: 182° – 185° C

Stability: Stable under ordinary conditions

Standards assay: 99.0% min.

Loss on drying: 0.5% max.

Residue on ignition: 0.1% max.

Heavy metals: 20 ppm max.

Pka: Bases at 8.75 and 7.09, acid at 4.82

Solubility: The solubility of the compound is pH dependent. The maximum aqueous solubility (40-60 mg/ml) occurs at a pH range of 2-5.

Dosage and administration: 200 mg and 400 mg daily oral; 40 ml (400 mg) single use intravenous; one drop every two h (0.3% w/v) daily as eye drops.

Mechanism of action
Gatifloxacin is an 8-methoxyfluoroquinolone with in vitro activity against a wide range of gram negative and gram positive microorganisms. The antibacterial action of gatifloxacin results from inhibition of DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division. It appears that the C-8-methoxy moiety contributes to enhanced activity and lower selection of resistant mutants of gram positive bacteria compared to the non methoxy C-8 moiety.

Pharmacokinetics

Absorption
Gatifloxacin is well absorbed from the gastrointestinal tract after oral administration and can be given without regard to food. Plasma concentrations of gatifloxacin
usually occur 1-2 h after oral dose. The absolute bioavailability of gatifloxacin tablets is 96%.

**Distribution**

Serum protein binding of gatifloxacin is approximately 20% in volunteers and is concentration independent. Rapid distribution of gatifloxacin into tissues results in higher gatifloxacin concentrations in most target tissues than in serum.

**Metabolism**

Gatifloxacin undergoes limited biotransformation in humans with less than 1% of the dose excreted in the urine as ethylenediamine metabolites.

**Excretion**

Gatifloxacin is excreted as unchanged drug primarily by the kidney. More than 70% of administered gatifloxacin dose was recovered as unchanged drug in the urine within 48 h following oral and intravenous administration and 5% was recovered in the feces. Less than 1% of the dose is recovered in the urine as two metabolites. Gatifloxacin undergoes both glomerular filtration and tubular secretion. Gatifloxacin may also undergo minimal biliary and/or intestinal elimination, since 5% of dose was recovered in the feces as unchanged drug.

**Half life**

Gatifloxacin has an elimination half life of about 7-10 h in body.

**Clearance**

Clearance rate of gatifloxacin is 124 to 161 ml/min

**Protein binding**

Serum protein binding of gatifloxacin is approximately 20%.

**Contraindications**

Gatifloxacin is contraindicated in persons with a history of hypersensitivity to gatifloxacin or any member of the quinolone class of antimicrobial agents. Gatifloxacin is contraindicated in patients with diabetes mellitus.
Warnings and precautions

Pregnancy
Because there are no adequate and well controlled studies in pregnant women, gatifloxacin solution should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.

Lactation
Gatifloxacin is distributed in rat’s milk. Since it is not known whether gatifloxacin distributed into milk in humans, caution is advised if the drug is administered in nursing women.

Pediatric use
Safety and effectiveness in infants below the age of one year has not been established.

Geriatric use
Serious disturbances of glucose homeostasis have been reported in elderly patients being treated with gatifloxacin.

Side effects (Related to eye) 82
Conjunctival irritation, eye pain, eye redness, papillary conjunctivitis, blurry vision, increased lacrimation, itching eyes, stringy mucus secretions, swelling of eye, eyelid or inner lining of eyelid, decrease in vision; swelling of the membrane covering the white part of the eye.

Drug interactions 83
Antidiabetic agents
Pharmacodynamic changes in glucose homeostasis were seen with concomitant administration of gatifloxacin and glyburide in patients with type 2 diabetes mellitus.

Nonsteroidal anti-inflammatory drugs (NSAIDS)
The concomitant administration of nonsteroidal anti-inflammatory drugs with a quinolone may increase the risks of CNS stimulation and convulsions.

Iron
When gatifloxacin (400 mg dose) was administered concomitantly with ferrous sulfate (single oral 325 mg dose), bioavailability of gatifloxacin was reduced.
Antacids
When gatifloxacin was administered 2 h before, concomitantly, or 2 after an aluminum/magnesium containing antacid, there was a reduction in bioavailability of gatifloxacin.

Probenecid
With concomitantly administrating gatifloxacin and probenecid, an increase in gatifloxacin AUC may cause glucose homeostasis abnormalities.

Uses
Gatifloxacin is a highly efficacious 8-methoxy fluoroquinolone which shows a broad spectrum of antibacterial activity, especially enhanced against gram-positive bacteria, including penicillin-resistant Streptococcus pneumoniae, as well as excellent activity against gram-negative and atypical organisms.

Gatifloxacin is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below

- Acute bacterial exacerbation of chronic bronchitis
- Acute sinusitis
- conjunctivitis
- Community acquired pneumonia
- Uncomplicated skin and skin structure infections (i.e., simple abscesses, furuncles, folliculitis, wound infections and cellulitis)
- Uncomplicated urinary tract infections (cystitis)
- Complicated urinary tract infections
- Pyelonephritis
- Uncomplicated urethral and cervical gonorrhea
- Uncomplicated rectal infections in women

Storage
Store at 15° to 25°C. Protect from freezing.
3.2.2 Moxifloxacin hydrochloride

**Structural formula**

![Structural formula of Moxifloxacin hydrochloride](image)

**Molecular formula**: C\textsubscript{21}H\textsubscript{24}FN\textsubscript{3}O\textsubscript{4}:HCl

**Category**: Flouroquinolone antibiotic

**Chemical name**: (4aS-cis)-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(octahydro-6H-pyrrolol[3,4-b]pyridin-6-yl)-4-oxo-3-quinolinecarboxylic acid monohydrochloride

**Molecular weight**: 437.89

**Description**: Slightly yellow to yellow crystalline powder.

**Brand names**: Actimax (Sankyo); Actira (Bayer); Avelox (Bayer); Octegra (Bayer); Proflox (Esteve); Vigamox (Alcon)

**Derivatives**: Moxifloxacin is a quinolone/fluoroquinolone antibiotic related to ciprofloxacin, enoxacin, fleroxacin, gatifloxacin, gemifloxacin, levofoxacin, lomefloxacin, norfloxacin, ofloxacin, pefloxacin, prulifloxacin, rufloxacin, sparflloxacin, temafloxacin, trovafloxacin, sitafloxacin

**Solubility**: Soluble in water, ethanol, 2-propanol and acetone

**Melting point**: 238 - 242°C
Dosage and administration: Oral- Tablets containing moxifloxacin hydrochloride (equivalent to 400 mg moxifloxacin). Parenteral- 250 ml latex-free flexibags as a sterile, preservative-free, 0.8% sodium chloride aqueous solution of moxifloxacin hydrochloride (containing 400 mg moxifloxacin). Ophthalmic (0.5% as eye drops)- Instill 1 drop in affected eyes 3 times daily for 7 days.

Description
Moxifloxacin is a fluoroquinolone anti-infective agent. Like other commercially available fluoroquinolones, moxifloxacin contains fluorine at the C 6 position of the quinolone nucleus. Moxifloxacin, like gatifloxacin, contains 8 methoxy group and has been termed 8 methoxy fluoroquinolone. The 8 methoxy and 7 diazabicyclo moieties on the quinolone nucleus of moxifloxacin appear to enhance activity against gram positive bacteria and decrease selection of resistant mutants in gram positive bacteria.85,86

Moxifloxacin is active in vitro and in clinical infections against most strains of Staphylococcus aureus (oxacillin susceptible strains only), Streptococcus pneumoniae (including penicillin resistant strains), S. pyogenes, Haemophilus influenzae, H. parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydia pneumoniae and Mycoplasma pneumoniae. Moxifloxacin also has in vitro activity against S. epidermidis (oxacillin susceptible strains only), S. agalactiae (group B streptococci), viridans streptococci, Citrobacter freundii, Enterobacter cloacae, Escherichia coli, K. oxytoca, Legionella pneumophila, Proteus mirabilis, Fusobacterium species, Peptostreptococcus species, and Prevotella species however, the safety and efficacy of moxifloxacin in treating clinical infections caused by these organisms have not been established in adequate and well controlled clinical trials to date. In addition, moxifloxacin is active in vitro against some mycobacteria, including Mycobacterium tuberculosis, M. avium complex (MAC), M. kansasii, and M. fortuitum and is active against some strains of M. tuberculosis resistant to isoniazid, rifampin or streptomycin.85,87,88
Moxifloxacin has greater activity in vitro against S. pneumoniae (including penicillin resistant strains) than many other fluoroquinolones (e.g. ciprofloxacin, levofloxacin, ofloxacin) while generally retaining the in vitro activity of these drugs against gram negative bacteria and etiologic agents of atypical pneumonia (e.g. Chlamydia pneumoniae, Mycoplasma pneumoniae, Legionella species). The relevance of these in vitro data to the treatment of clinical infections remains to be determined. Cross resistance can occur between moxifloxacin and other fluoroquinolones in gram negative bacteria, but some gram positive bacteria resistant to other fluoroquinolones may be susceptible to moxifloxacin.\textsuperscript{85}

**Antimicrobial action**

Moxifloxacin (MOXI: 8-methoxy-quinolone) and quinolones in general, exert their effects by trapping a DNA drug enzyme complex and specifically inhibiting ATP dependent enzymes topoisomerase II (DNA gyrase) and topoisomerase IV. In most bacteria gyrase facilitates DNA unwinding and topoisomerase IV activates decatenation. DNA gyrase an essential enzyme involved in the replication, transcription and repair of bacterial DNA, consists of two components arranged in a GyrA2/GyrB2 complex encoded by the gyrA and gyrB genes. Topoisomerase IV, encoded by par C and par E, appears to be absent from Mycobacterium tuberculosis and from several other bacteria including Helicobacter pylori and Treponema palladium. Recently the single M. tuberculosis type II topoisomerase has been cloned into Escherichia coli and exhibits classical supercoiling activity as well as enhanced decatenation, cleavage and relaxation activities. This is presumably the single target for MOXI in the mycobacteria.\textsuperscript{85}

**Pharmacokinetics**

Moxifloxacin is well absorbed following oral administration, having an absolute bioavailability of approximately 90%. The drug has a serum elimination half-life of about 12–15 h allowing once daily dosing. Moxifloxacin is metabolized principally via sulfate and glucuronide conjugation; the drug is not metabolized by and does not appear to affect the cytochrome P-450 (CYP) enzyme system.\textsuperscript{85,89,90}
Absorption
Bioavailability is 86–92%. Peak plasma concentrations attained within 0.5–4 h; steady state attained after at least 3 days. High fat meals do not affect absorption. Yogurt does not affect rate or extent of absorption.

Distribution
Widely distributed into body tissues and fluids, including saliva, nasal, bronchial secretions, sinus mucosa, skin blister fluid, subcutaneous tissue and muscle. Distributed into milk of rats and may also be distributed into human milk. Plasma protein binding is 45–50%.

Elimination
Approximately 52% of an oral or IV dose is metabolized via glucuronide and sulfate conjugation; the metabolites are not microbiologically active. Not metabolized by CYP isoenzymes. Eliminated in urine and by biliary excretion and metabolism. Approximately 45% of an oral or IV dose excreted unchanged (20% in urine and 25% in feces). A total of 96% of an oral dose is excreted as unchanged drug or metabolites.

Half life
Adult with normal renal and hepatic function, approximately 12 h.

Warning and precaution
General
- As with other anti infectives, prolonged use may result in overgrowth of non susceptible organisms, including fungi. If super infection occurs, discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and where appropriate, fluorescein staining. Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long term studies in animals to determine the carcinogenic potential of moxifloxacin have not been performed. However, in an accelerated study with initiators and promoters, moxifloxacin was not carcinogenic in rats following up to 38 weeks of oral dosing at 500 mg/kg/day (approximately 21,700 times the highest recommended total daily human ophthalmic dose for a 50 kg person, on a mg/kg basis). Moxifloxacin
was not mutagenic in four bacterial strains used in the Ames Salmonella reversion assay. As with other quinolones, the positive response observed with moxifloxacin in strain TA 102 using the same assay may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay. An equivocal result was obtained in the same assay when v79 cells were used. Moxifloxacin was clastogenic in the v79 chromosome aberration assay, but it did not induce unscheduled DNA synthesis in cultured rat hepatocytes. There was no evidence of genotoxicity in vivo in a micronucleus test or a dominant lethal test in mice.

Moxifloxacin had no effect on fertility in male and female rats at oral doses as high as 500 mg/kg/day, approximately 21,700 times the highest recommended total daily human ophthalmic dose. At 500 mg/kg orally there are slight effects on sperm morphology (head tail separation) in male rats and on the estrous cycle in female rats.

**Pregnancy**

Moxifloxacin was not teratogenic when administered to pregnant rats during organogenesis at oral doses as high as 500 mg/kg/day (approximately 21,700 times the highest recommended total daily human ophthalmic dose); however, decreased fetal body weights and slightly delayed fetal skeletal development were observed. There was no evidence of teratogenicity when pregnant cynomolgus monkeys were given oral doses as high as 100 mg/kg/day (approximately 4,300 times the highest recommended total daily human ophthalmic dose). An increased incidence of smaller fetuses was observed at 100 mg/kg/day. Since there are no adequate and well controlled studies in pregnant women, moxifloxacin solution (0.5%) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing mothers**

Moxifloxacin has not been measured in human milk, although it can be presumed to be excreted in human milk. Caution should be exercised when moxifloxacin solution (0.5%) solution is administered to a nursing mother.

**Pediatric use**

The safety and effectiveness of moxifloxacin solution in infants below 1 year of age have not been established. There is no evidence that the ophthalmic administration of moxifloxacin solution has any effect on weight bearing joints, even though oral
administration of some quinolones has been shown to cause arthropathy in immature animals.

**Geriatric use**
No overall differences in safety and effectiveness have been observed between elderly and younger patients.91

**Side effects**
The most frequently reported ocular adverse events were conjunctivitis, decreased visual acuity, dry eye, keratitis, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, subconjunctival hemorrhage and tearing. These events occurred in approximately 1-6% of patients. Nonocular adverse events reported at a rate of 1-4% were fever, increased cough, infection, otitis media, pharyngitis, rash and rhinitis.91

**Drug interactions**

**Antacids**
Moxifloxacin should be taken at least 4 h before or 8 h after antacids that contain aluminum, calcium, or magnesium.

**Didanosine**
If given concomitantly, buffered didanosine preparations (chewable/dispersible buffered tablets, buffered powder for oral solution or unbuffered pediatric powder for oral solution prepared as an admixture with antacid) should be taken at least 4 h before or 8 h after moxifloxacin.

**Digoxin, Glyburide, Probenecid, Ranitidine, and Theophylline**
Pharmacokinetic interaction with iron, multivitamins, mineral supplements and Sucralfate, pharmacokinetic interaction (decreased oral absorption), if given concomitantly, these drugs should be taken at least 4 h before or 8 h after moxifloxacin.

**Nonsteroidal anti-inflammatory agents**
The concomitant administration of nonsteroidal anti-inflammatory drugs with a quinolone may increase the risks of CNS stimulation and convulsions.

**Warfarin**
Increased prothrombin time/international normalized ratio (INR) and enhanced anticoagulant effects reported with some other quinolones (e.g., norfloxacin). While
no clinically important effect of moxifloxacin on R- and S-warfarin or prothrombin time was detected in a study in healthy individuals, the manufacturer recommends careful monitoring of prothrombin time/coagulation tests in patients receiving concomitant warfarin and moxifloxacin.85

Uses92
Moxifloxacin hydrochloride is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below

- Respiratory tract infections (acute sinusitis, acute exacerbations of chronic bronchitis, community acquired pneumonia)
- Ophthalmic infection (conjunctivitis, keratitis and keratoconjunctivitis) caused by susceptible organisms
- Uncomplicated skin and skin structure infections caused by susceptible bacteria
- Uncomplicated abscesses, furuncles, cellulites, impetigo and other skin infections.
- For treatment of inhalational anthrax
- Active tuberculosis in patients with infections caused by Mycobacterium tuberculosis
- Post exposure prophylaxis following suspected or confirmed exposure to aerosolized anthrax spores
- Uncomplicated urinary tract infections (cystitis).85

Storage
Store ophthalmic solution at 2°C to 25°C.91

3.3. POLYMERS PROFILE
3.3.1 Hydroxypropyl methylcellulose93,94 (HPMC)

Synonyms
Hypromellose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose.

Chemical name
Cellulose hydroxypropyl methyl ether.
**Review of literature**

**Structural formula**

![Structural formula](image)

**Description**

It is a white or grayish white practically odorless, hygroscopic powder or granules.

**Functional categories**

Suspending, Viscosity increasing agent, Binder, Coating agent, Film former and emulsion stabilizer.

**Solubility**

Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.

**Viscosity**

A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. Dichloromethane and ethanol mixtures may also be used to prepare viscous hypromellose solutions. Solutions prepared using organic solvents tend to be more viscous; increasing concentration also produces more viscous solutions. To prepare an aqueous solution, it is recommended that hypromellose is dispersed and thoroughly hydrated in about 20–30% of the required amount of water. The water should be vigorously stirred and heated to 80–90°C, then the remaining hypromellose should be added. Sufficient cold water should then be added to produce the required volume.
Table 3.1 Typical viscosity values for 2% w/v aqueous solutions of methocel at 20°C

<table>
<thead>
<tr>
<th>HPMC product</th>
<th>Nominal viscosity (mPa s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methocel K100 Premium LVEP</td>
<td>100</td>
</tr>
<tr>
<td>Methocel K4M Premium</td>
<td>4000</td>
</tr>
<tr>
<td>Methocel K15M Premium</td>
<td>15 000</td>
</tr>
<tr>
<td>Methocel K100M Premium</td>
<td>100 000</td>
</tr>
<tr>
<td>Methocel E4M Premium</td>
<td>4000</td>
</tr>
<tr>
<td>Methocel F50 Premium</td>
<td>50</td>
</tr>
<tr>
<td>Methocel E10M Premium CR</td>
<td>10 000</td>
</tr>
<tr>
<td>Methocel E3 Premium LV</td>
<td>3</td>
</tr>
<tr>
<td>Methocel E5 Premium LV</td>
<td>5</td>
</tr>
<tr>
<td>Methocel E6 Premium LV</td>
<td>6</td>
</tr>
<tr>
<td>Methocel E15 Premium LV</td>
<td>15</td>
</tr>
<tr>
<td>Methocel E50 Premium LV</td>
<td>50</td>
</tr>
</tbody>
</table>

When a water miscible organic solvent such as ethanol (95%), glycol or mixtures of ethanol and dichloromethane are used, the hypromellose should first be dispersed into the organic solvent, at a ratio of 5–8 parts of solvent to 1 part of hypromellose. Cold water is then added to produce the required volume.

**Stability and storage conditions**

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol to gel transformation upon heating and cooling, respectively. The gel point is 50–90°C, depending upon the grade and concentration of material. Aqueous solutions are comparatively enzyme resistant, providing good viscosity stability during long term storage. However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative. When hypromellose is used as a viscosity-increasing agent in ophthalmic solutions, benzalkonium chloride is commonly used as the preservative. Aqueous solutions may also be sterilized by autoclaving and the coagulated polymer...
must be redispersed on cooling by shaking. Hypromellose powder should be stored in a well closed container, in a cool, dry place.

Incompatibilities
Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

Safety
Hypromellose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products. Hypromellose is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may have a laxative effect. The WHO has not specified an acceptable daily intake for hypromellose since the levels consumed were not considered to represent a hazard to health.96

Applications
Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations.

• In oral products, hypromellose is primarily used as a tablet binder,97 in film coating,98 and as a matrix for use in extended release tablet formulations.99 Concentrations between 2% and 5% w/w may be used as a binder in either wet or dry granulation processes. High viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules.

• Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film forming solutions to film-coat tablets. Lower viscosity grades are used in aqueous film coating solutions, while higher viscosity grades are used with organic solvents. Examples of filmcoating materials that are commercially available include AnyCoat C, Spectracel, and Pharmacoat. Hypromellose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undispersed fibers present and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.
• Hypromellose is also used as an emulsifier, suspending agent and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

• In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

• Ophthalmic use: Hypromellose solutions are semisynthetic substitute for tear-film. Its molecular structure is predicated upon a base celluloid compound that is highly water soluble. Post application, celluloid attributes of good water solubility reportedly aids in visual clarity. When applied, a hypromellose solution acts to swell and absorb water, thereby expanding the thickness of the tear-film. Hypromellose augmentation therefore results in extended lubricant time presence on the cornea, which theoretically results in decreased eye irritation, especially in dry climates, home or work environments. Hypromellose 2% solution has been documented to be used during surgery to aid in corneal protection and during orbital surgery.

3.3.2 Methyl Cellulose\textsuperscript{100} (MC)

Synonyms
Benecel; Culminial MC; Metolose.

Chemical name
Cellulose methyl ether

Structural formula

\[
\begin{array}{c}
\text{\textbf{3.3.2 Methyl Cellulose\textsuperscript{100} (MC)}} \\
\text{Synonyms} \\
\text{Benecel; Culminial MC; Metolose.} \\
\text{Chemical name} \\
\text{Cellulose methyl ether} \\
\text{Structural formula}
\end{array}
\]
Description
Methylcellulose occurs as a white, fibrous powder or granules. It is practically odorless and tasteless. It should be labeled to indicate its viscosity type (viscosity of a 1 in 50 solution).

Functional categories
Coating agent; emulsifying agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity increasing agent.

Solubility
Practically insoluble in acetone, methanol, chloroform, ethanol (95%), ether, saturated salt solutions, toluene and hot water. Soluble in glacial acetic acid and in a mixture of equal volumes of ethanol and chloroform. In cold water, methylcellulose swells and disperses slowly to form a clear to opalescent, viscous, colloidal dispersion.

Viscosity
Various grades of methylcellulose are commercially available that vary in their degree of polymerization. Aqueous solutions at concentrations of 2% w/v will produce viscosities between 5 and 75 000 mPa s. Individual grades of methylcellulose have a stated, narrowly defined viscosity range measured for a 2% w/v solution. The viscosity of solutions may be increased by increasing the concentration of methylcellulose. Increased temperatures reduce the viscosity of solutions until gel formation occurs at 50–60°C. The process of thermogelation is reversible, with a viscous solution being reformed on cooling.

Table 3.2 Typical viscosity values for 2% w/v aqueous solutions of MC at 20°C

<table>
<thead>
<tr>
<th>Methocel grade</th>
<th>Viscosity (mPa s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A4MP</td>
<td>4000</td>
</tr>
<tr>
<td>A15-LV</td>
<td>15</td>
</tr>
<tr>
<td>A15CP</td>
<td>1500</td>
</tr>
<tr>
<td>A4CP</td>
<td>400</td>
</tr>
</tbody>
</table>

Stability and storage conditions
Methylcellulose powder is stable, although slightly hygroscopic. The bulk material should be stored in an airtight container in a cool, dry place. Solutions of methylcellulose are stable to alkalis and dilute acids at pH 3–11, at room temperature.
At pH less than 3, acid-catalyzed hydrolysis of the glucose-glucose linkages occurs and the viscosity of methylcellulose solutions is reduced. On heating, solution viscosity is reduced until gel formation occurs at approximately 50°C. Methylcellulose solutions are liable to microbial spoilage and antimicrobial preservatives should therefore be used. Solutions may also be sterilized by autoclaving, although this process can decrease the viscosity of a solution. The change in viscosity after autoclaving is related to solution pH. Solutions at pH less than 4 had viscosities reduced by more than 20% subsequent to autoclaving. 

**Incompatibilities**

Methylcellulose is incompatible with aminacrine hydrochloride, chlorocresol, mercuric chloride, phenol, resorcinol, tannic acid, silver nitrate, cetylpyridinium chloride, p-hydroxybenzoic acid, p-aminobenzoic acid, methylparaben, propylparaben and butylparaben. Salts of mineral acids (particularly polybasic acids), phenols and tannins will coagulate solutions of methylcellulose, although this can be prevented by the addition of ethanol (95%) or glycol diacetate. Complexation of methylcellulose occurs with highly surface active compounds such as tetracaine and dibutoline sulfate. High concentrations of electrolytes increase the viscosity of methylcellulose mucilages owing to the ‘salting out’ of methylcellulose. With very high concentrations of electrolytes, the methylcellulose may be completely precipitated in the form of a discrete or continuous gel. Methylcellulose is incompatible with strong oxidizing agents.

**Safety**

Methylcellulose is widely used in a variety of oral and topical pharmaceutical formulations. It is also extensively used in cosmetics and food products and is generally regarded as a nontoxic, nonallergenic and nonirritant material. Following oral consumption, methylcellulose is not digested or absorbed and is therefore a noncaloric material. Ingestion of excessive amounts of methylcellulose may temporarily increase flatulence and gastrointestinal distension. In the normal individual, oral consumption of large amounts of methylcellulose has a laxative action and medium or high viscosity grades are therefore used as bulk laxatives.

Esophageal obstruction may occur if methylcellulose is swallowed with an insufficient quantity of liquid. Consumption of large quantities of methylcellulose
may additionally interfere with the normal absorption of some minerals. However, this and the other adverse effects discussed above relate mainly to the use of methylcellulose as a bulk laxative and are not significant factors when methylcellulose is used as an excipient in oral preparations. Methylcellulose is not commonly used in parenteral products, although it has been used in intraarticular and intramuscular injections. Studies in rats have suggested that parenterally administered methylcellulose may cause glomerulonephritis and hypertension.\textsuperscript{95}

The WHO has not specified an acceptable daily intake of methylcellulose since the level of use in foods was not considered to be a hazard to health.

**Applications**

Methylcellulose is widely used in oral and topical pharmaceutical formulations.

**Table 3.3 Use of Methylcellulose**

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk laxative</td>
<td>5.0–30.0</td>
</tr>
<tr>
<td>Creams, gels, and ointments</td>
<td>1.0–5.0</td>
</tr>
<tr>
<td>Emulsifying agent</td>
<td>1.0–5.0</td>
</tr>
<tr>
<td>Ophthalmic preparations</td>
<td>0.5–1.0</td>
</tr>
<tr>
<td>Suspensions</td>
<td>1.0–2.0</td>
</tr>
<tr>
<td>Sustained-release tablet matrix</td>
<td>5.0–75.0</td>
</tr>
<tr>
<td>Tablet binder</td>
<td>1.0–5.0</td>
</tr>
<tr>
<td>Tablet disintegrant</td>
<td>2.0–10.0</td>
</tr>
</tbody>
</table>

- In tablet formulations, low or medium viscosity grades of methylcellulose are used as binding agents, the methylcellulose being added either as a dry powder or in solution. High viscosity grades of methylcellulose may also be incorporated in tablet formulations as a disintegrant. Methylcellulose may be added to a tablet formulation to produce sustained release preparations.

- Tablet cores may also be spray coated with either aqueous or organic solutions of highly substituted low viscosity grades of methylcellulose to mask an unpleasant taste or to modify the release of a drug by controlling the physical nature of the granules. Methylcellulose coats are also used for sealing tablet cores prior to sugar coating.
• Low viscosity grades of methylcellulose are used to emulsify olive, peanut, and mineral oils. They are also used as suspending or thickening agents for orally administered liquids, methylcellulose commonly being used in place of sugar based syrups or other suspension bases. Methylcellulose delays the settling of suspensions and increases the contact time of drugs, such as antacids, in the stomach.

• High viscosity grades of methylcellulose are used to thicken topically applied products such as creams and gels.

• In ophthalmic preparations, a 0.5–1.0% w/v solution of a highly substituted, high viscosity grade of methylcellulose has been used as a vehicle for eye drops. However, hypromellose based formulations are now preferred for ophthalmic preparations.102

• Therapeutically, methylcellulose is used as a bulk laxative. It has also been used to aid appetite control in the management of obesity, but there is little evidence supporting its efficacy.

3.3.3 Polyvinyl pyrrolidone103

Synonyms
Poly [1-(2-oxo-1-pyrrolidinyl) ethylene]; polyvidone; povidone; PVP; 1-vinyl-2-pyrrolidinone polymer.

Chemical name
1-Ethenyl-2-pyrrolidinone homopolymer.

Structural formula

\[
\text{\begin{array}{c}
\text{N} \\
\text{C} - \text{C} \ 	ext{CH} - \text{CH}_2 \\
\end{array}}
\]

Description
Povidone occurs as a fine, white to creamy white colored, odorless or almost odorless, hygroscopic powder.
Functional categories
Disintegrant; dissolution aid; suspending agent; tablet binder.

Solubility
Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol and water; practically insoluble in ether, hydrocarbons and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the K-value.

Molecular weight
The USP 28 describes povidone as a synthetic polymer consisting essentially of linear 1- vinyl-2-pyrrolidinone groups, the differing degree of polymerization of which results in polymers of various molecular weights. Approximate molecular weights for different povidone grades are shown in Table 3.4

Table 3.4 Approximate molecular weights for different grades of povidone

<table>
<thead>
<tr>
<th>$\nu$-value</th>
<th>Approximate molecular weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>2 500</td>
</tr>
<tr>
<td>15</td>
<td>8 000</td>
</tr>
<tr>
<td>17</td>
<td>10 000</td>
</tr>
<tr>
<td>25</td>
<td>30 000</td>
</tr>
<tr>
<td>30</td>
<td>50 000</td>
</tr>
<tr>
<td>60</td>
<td>400 000</td>
</tr>
</tbody>
</table>

Stability and storage condition
Povidone darkens to some extent on heating at $150^\circ C$, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around $110-130^\circ C$; steam sterilization of an aqueous solution does not alter its properties. Aqueous solutions are susceptible to mold growth and consequently require the addition of suitable preservatives.

Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.
Incompatibilities
Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin and other compounds. The efficacy of some preservatives, e.g. thimerosal, may be adversely affected by the formation of complexes with povidone.

Safety
Povidone is widely used as an excipient, particularly in oral tablets and solutions. When consumed orally, povidone may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes. Povidone additionally has no irritant effect on the skin and causes no sensitization. No eye irritation or allergies, the actual non toxic.

Applications
• Povidone is used in a variety of pharmaceutical formulations; it is primarily used in solid dosage forms. In tableting, povidone solutions are used as binders in wet granulation processes.\(^\text{104}\)

• Povidone is also added to powder blends in the dry form and granulated \textit{in situ} by the addition of water, alcohol or hydroalcoholic solutions.

• Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid dosage forms.

• Povidone solutions may also be used as coating agents. It is additionally used as a suspending, stabilizing or viscosity increasing agent in a number of topical and oral suspensions and solutions.

• Povidone solution are very stable, film forming and its film colorless transparent, hard and bright.

Table 3.5 Use of povidone

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrier for drugs</td>
<td>10–25</td>
</tr>
<tr>
<td>Dispersing agent</td>
<td>Up to 5</td>
</tr>
<tr>
<td>Eye drops</td>
<td>2–10</td>
</tr>
<tr>
<td>Suspending agent</td>
<td>Up to 5</td>
</tr>
<tr>
<td>Tablet binder, tablet diluent, or coating agent</td>
<td>0.5–5</td>
</tr>
</tbody>
</table>
3.3.4 Polyvinyl alcohol

Synonyms
Polyvinol; PVA; vinyl alcohol polymer.

Chemical name
Ethenol, homopolymer.

Structural formula

\[
\text{CH}_2\text{CH} \quad \text{OH}
\]

Description
Occurs as an odorless, white to cream colored granular powder.

Functional categories
Suspending, viscosity increasing agent, binder, coating agent, film former and emulsion stabilizer.

Solubility
Essentially soluble in hot or cold water, partially soluble in some polyhydroxy compounds, certain amines and amides, practically insoluble in aliphatic, aromatic and chlorinated hydrocarbons, esters, ketones and oils.

Molecular weight
A molecular weight range of approximately 20000–290000

<table>
<thead>
<tr>
<th>Grade</th>
<th>Molecular weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>High viscosity</td>
<td>~200 000</td>
</tr>
<tr>
<td>Medium viscosity</td>
<td>~130 000</td>
</tr>
<tr>
<td>Low viscosity</td>
<td>~20 000</td>
</tr>
</tbody>
</table>
Stability and storage condition
Polyvinyl alcohol is stable when stored in a tightly sealed container in a cool, dry place. Aqueous solutions are stable in corrosion resistant sealed containers. Preservatives may be added to the solution if extended storage is required. Polyvinyl alcohol undergoes slow degradation at 100°C and rapid degradation at 200°C; it is stable on exposure to light.

Incompatibilities
Polyvinyl alcohol undergoes reactions typical of a compound with secondary hydroxy groups, such as esterification. It decomposes in strong acids and softens or dissolves in weak acids and alkalis. It is incompatible at high concentration with inorganic salts, especially sulfates and phosphates; precipitation of polyvinyl alcohol 5% w/v can be caused by phosphates. Gelling of polyvinyl alcohol solution may occur if borax is present.

Safety and application
Nontoxic when applied to eye or skin, no irritation up to 10%.

Applications
- Polyvinyl alcohol is used primarily in topical pharmaceutical and ophthalmic formulations.
- It is used as a stabilizing agent for emulsions (0.25–3.0% w/v). Polyvinyl alcohol is also used as a viscosity increasing agent for ophthalmic products.
- It is used in artificial tears and contact lens solutions for lubrication purposes, in sustained release formulations for oral administration and in transdermal patches. Polyvinyl alcohol may be made into microspheres when mixed with a glutaraldehyde solution.109

Table 3.7 Use of polyvinyl alcohol

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emulsions</td>
<td>0.5</td>
</tr>
<tr>
<td>Ophthalmic formulations</td>
<td>0.25–3.00</td>
</tr>
<tr>
<td>Topical lotions</td>
<td>2.5</td>
</tr>
</tbody>
</table>
3.3.5 EthylCellulose (Cellulose, Ethyl ether, Ethocel)\textsuperscript{107}

Synonyms
Aquacoat ECD; Aqualon; Ethocel; Surelease.

Chemical name
Cellulose ethyl ether.

Structural formula

\[
\text{CH}_2\text{C}_8\text{H}_{15}
\]

Description
It is a white, odourless, tasteless and free flowing powder. It is white to light tan powder.

Functional category
Coating agent; flavoring fixative; tablet binder; tablet filler; viscosity increasing agent.

Solubility
Insoluble in water, glycerin and propylene glycol but soluble in varying degrees in certain organic solvents, depending upon their ethoxyl content. The addition of 19-20\% of a lower aliphatic alcohol to solvents, such as ketones, esters and hydrocarbons can improve the solubility.

Viscosity
The viscosity of ethylcellulose is measured typically at 25\(^\circ\)C using 5\% w/v ethylcellulose dissolved in a solvent blend of 80\% toluene and 20\% ethanol (w/w). Grades of ethylcellulose with various viscosities are commercially available (Table 3.8). They may be used to produce 5\% w/v solutions in organic solvent blends with
viscosities nominally ranging from 7 to 100 mPa s (7-100 cp). Specific ethylcellulose grades or blends of different grades, may be used to obtain solutions of a desired viscosity. Solutions of higher viscosity tend to be composed of longer polymer chains and produce strong and durable films. The viscosity of an ethylcellulose solution increases with an increase in ethylcellulose concentration e.g. the viscosity of a 5% w/v solution of Ethocel Standard 4 Premium is 4 mPa s (4 cp) and of a 25% w/v solution of the same ethylcellulose grade is 850 mPa s (850 cp).

Table 3.8 Viscosity of ethylcellulose with different grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Solution viscosity (mPa s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethocel Std 4 Premium</td>
<td>3.0–5.5</td>
</tr>
<tr>
<td>N-7</td>
<td>5.6–8.0</td>
</tr>
<tr>
<td>Ethocel Std 7FP Premium</td>
<td>6.0–8.0</td>
</tr>
<tr>
<td>Ethocel Std 10FP Premium</td>
<td>9.0–11.0</td>
</tr>
<tr>
<td>N-14</td>
<td>12.0–16.0</td>
</tr>
<tr>
<td>Ethocel Std 20P Premium</td>
<td>18.0–22.0</td>
</tr>
<tr>
<td>Ethocel Std 45P Premium</td>
<td>41.0–49.0</td>
</tr>
</tbody>
</table>

Stability and storage conditions
Ethylcellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalis, both dilute and concentrated and to salt solutions, although it is more sensitive to acidic materials than are cellulose esters.

Ethylcellulose is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. This may be prevented by the use of antioxidant and chemical additives that absorb light in the 230–340 nm range. It should be stored at a temperature not exceeding 32°C in a dry area away from all sources of heat. It should not be stored next to peroxides or other oxidizing agent.

Incompatibilities
Incompatible with paraffin wax and microcrystalline wax.

Safety
Ethylcellulose is widely used in oral and topical pharmaceutical formulations. It is also used in food products. Ethylcellulose is not metabolized following oral consumption and is therefore a noncalorific substance. Because ethylcellulose is not metabolized it is not recommended for parenteral products; parenteral use may be
harmful to the kidneys. Ethylcellulose is generally regarded as a nontoxic, nonallergenic and nonirritating material.

Applications
Ethylcellulose is widely used in oral and topical pharmaceutical formulations

- The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets and granules. Ethylcellulose coatings are used to modify the release of a drug to mask an unpleasant taste or to improve the stability of a formulation; for example, where granules are coated with ethylcellulose to inhibit oxidation. Modified release tablet formulations may also be produced using ethylcellulose as a matrix former.

- Ethylcellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water insoluble films. Higher viscosity ethylcellulose grades tend to produce stronger and more durable films. Ethylcellulose films may be modified to alter their solubility, by the addition of hypromellose or a plasticizer.

- Drug release through ethylcellulose-coated dosage forms can be controlled by diffusion through the film coating. This can be a slow process unless a large surface area (e.g. pellets or granules compared with tablets) is utilized. In those instances, aqueous ethylcellulose dispersions are generally used to coat granules or pellets. Ethylcellulose-coated beads and granules have also demonstrated the ability to absorb pressure and hence protect the coating from fracture during compression.

- High viscosity grades of ethylcellulose are used in drug microencapsulation.

- In tablet formulations, ethylcellulose may additionally be employed as a binder, the ethylcellulose being blended dry or wet granulated with a solvent such as ethanol (95%). Ethylcellulose produces hard tablets with low friability, although they may demonstrate poor dissolution.
Table 3.9 Use of ethyl cellulose

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microencapsulation</td>
<td>10.0–20.0</td>
</tr>
<tr>
<td>Sustained release tablet coating</td>
<td>3.0–20.0</td>
</tr>
<tr>
<td>Tablet coating</td>
<td>1.0–3.0</td>
</tr>
<tr>
<td>Tablet granulation</td>
<td>1.0–3.0</td>
</tr>
</tbody>
</table>

3.3.6 Gelatin\textsuperscript{108,109}

**Synonyms**
Byco; Cryogel; gelatine; Instagel; Solugel.

**Chemical name**
Gelatin [9000-70-8]

**Description**
Gelatin occurs as a light-amber to faintly yellow-colored, vitreous, brittle solid. It is practically odorless and tasteless and is available as translucent sheets and granules, or as a powder.

**Functional category**
Coating agent; film-former; gelling agent; suspending agent; tablet binder; viscosity increasing agent.

**Solubility**
Practically insoluble in acetone, chloroform, ethanol (95%), ether and methanol. Soluble in glycerin, acids and alkalis, although strong acids or alkalis cause precipitation. In water, gelatin swells and softens, gradually absorbing between five and 10 times its own weight of water. Gelatin is soluble in hot water, forming a jelly, or gel, on cooling to 35–40°C. At temperatures >40°C, the system exists as a sol. This gel to sol system is heat reversible, the melting temperature being slightly higher than the setting point; the melting point can be varied by the addition of glycerin.

**Viscosity**
4.3–4.7 mPa s (4.3–4.7 cp) for a 6.67% w/v aqueous solution at 60°C; 18.5–20.5 mPas (18.5–20.5 cp) for a 12.5% w/v aqueous solution at 60°C.
Stability and storage conditions
Dry gelatin is stable in air. Aqueous gelatin solutions are also stable for long periods if stored under cool, sterile conditions. At temperatures above about 50°C, aqueous gelatin solutions may undergo slow depolymerization and a reduction in gel strength may occur on resetting. Depolymerization becomes more rapid at temperatures above 65°C and gel strength may be reduced by half when a solution is heated at 80°C for 1 hour. The rate and extent of depolymerization depends on the molecular weight of the gelatin, with a lower-molecular weight material decomposing more rapidly. The bulk material should be stored in an airtight container in a cool, dry place.

Incompatibilities
Gelatin is an amphoteric material and will react with both acids and bases. It is also a protein and thus exhibits chemical properties characteristic of such materials; for example, gelatin may be hydrolyzed by most proteolytic systems to yield its amino acid components. Gelatin will also react with aldehydes and aldehydic sugars, anionic and cationic polymers, electrolytes, metal ions, plasticizers, preservatives and surfactants. It is precipitated by alcohols, chloroform, ether, mercury salts and tannic acid. Gels can be liquefied by bacteria unless preserved.

Safety
Gelatin is widely used in a variety of pharmaceutical formulations including oral and parenteral products. In general, when used in oral formulations gelatin may be regarded as a nontoxic and nonirritant material. However, there have been rare reports of gelatin capsules adhering to the esophageal lining, which may cause local irritation. Hypersensitivity reactions, including serious anaphylactic reactions, have been reported following the use of gelatin in parenteral products.

Applications
- Gelatin is widely used in a variety of pharmaceutical formulations, including its use as a biodegradable matrix material in an implantable delivery system, although it is most frequently used to form either hard or soft gelatin capsules.
- Gelatin capsules are unit dosage forms that are filled with an active drug and are generally designed for oral administration. Although gelatin is poorly soluble in
cold water, a gelatin capsule will swell in gastric fluid to rapidly release its contents.

- Soft gelatin capsules are formed from an aqueous gelatin solution that contains a plasticizer such as glycerin or sorbitol. Two soft gelatin strips are formed that run between suitable dies. As the dies meet, capsules are formed by injecting the filling material, followed by the capsule halves being sealed together.

- Gelatin is also used for the microencapsulation of drugs, where the active drug is sealed inside a microsized capsule or beadlet, which may then be handled as a powder. The first microencapsulated drugs (beadlets) were fish oils and oily vitamins in gelatin beadlets prepared by an emulsion process.

- Therapeutically, gelatin has been used in the preparation of wound dressings and has been used as a plasma substitute, although anaphylactoid reactions have been reported in the latter application. Absorbable gelatin is available as sterile film, ophthalmic film, sterile sponge, sterile compressed sponge and sterile powder from sponge. Gelatin sponge has hemostatic properties.

3.4 PLASTICIZERS PROFILE

3.4.1 Polyethylene glycol

Synonyms
Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; PEG; Pluriol E; polyoxyethylene glycol.

Chemical name
α-Hydro-o-hydroxypoly(oxy-1,2-ethanediyl).

Structural formula

\[
\text{HO} \quad \text{C} \quad (\text{CH}_2 \quad \text{O} \quad \text{CH}_2)_m \quad \text{C} \quad \text{OH}
\]
Description
Light PEG'S (Grades 200-600). Clear, colorless or slightly yellowish viscous liquid. The odor is slight but characteristic and the taste is bitter and slightly burning.

Functional categories
Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

Solubility
All grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary). Aqueous solutions of higher-molecular-weight grades may form gels. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%) and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

Viscosity and density

<table>
<thead>
<tr>
<th>Type of PEG</th>
<th>Density (g/cm³)</th>
<th>Viscosity (dynamic) [mPa s (cp)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>1.120</td>
<td>80–105</td>
</tr>
<tr>
<td>400</td>
<td>1.120</td>
<td>105–130</td>
</tr>
<tr>
<td>600</td>
<td>1.080</td>
<td>15–20</td>
</tr>
<tr>
<td>1000</td>
<td>1.080</td>
<td>22–30</td>
</tr>
<tr>
<td>1500</td>
<td>1.080</td>
<td>34–50</td>
</tr>
<tr>
<td>3000</td>
<td>1.080</td>
<td>75–100</td>
</tr>
<tr>
<td>3350</td>
<td>1.080</td>
<td>83–120</td>
</tr>
<tr>
<td>4000</td>
<td>1.080</td>
<td>110–170</td>
</tr>
<tr>
<td>6000</td>
<td>1.080</td>
<td>200–270</td>
</tr>
<tr>
<td>8000</td>
<td>1.080</td>
<td>260–510</td>
</tr>
</tbody>
</table>

Safety
Polyethylene glycols are widely used in a variety of pharmaceutical formulations. Generally, they are regarded as nontoxic and nonirritant materials.
Stability and storage
Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, and they do not become rancid. Polyethylene glycols and aqueous polyethylene glycol solutions can be sterilized by autoclaving, filtration or gamma irradiation. Polyethylene glycols should be stored in well closed containers in a cool, dry place. Stainless steel, aluminum, glass or lined steel containers are preferred for the storage of liquid grades.

Incompatibilities
The chemical reactivity of polyethylene glycols is mainly confined to the two terminal hydroxyl groups, which can be either esterified or etherified. However, all grades can exhibit some oxidizing activity owing to the presence of peroxide impurities and secondary products formed by autoxidation. Physical effects caused by polyethylene glycol bases include softening and liquefaction in mixtures with phenol, tannic acid and salicylic acid. Discoloration of sulfonamides and dithranol can also occur and sorbitol may be precipitated from mixtures.

Applications
Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral and rectal preparations. It has been used experimentally in biodegradable polymeric matrices used in controlled release systems.

- Solid grades are generally employed in topical ointments, with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol.

- Mixtures of polyethylene glycols can be used as suppository bases.

- Aqueous polyethylene glycol solutions can be used either as suspending agents or to adjust the viscosity and consistency of other suspending vehicles. When used in conjunction with other emulsifiers, polyethylene glycols can act as emulsion stabilizers.

- In film coatings, solid grades of polyethylene glycol can be used alone for the film coating of tablets or can be useful as hydrophilic polishing materials.
• Liquid grades are also widely used as plasticizers in conjunction with film forming polymers.

• Polyethylene glycols are useful as plasticizers in microencapsulated products to avoid rupture of the coating film when the microcapsules are compressed into tablets.

3.4.2. Glycerin\textsuperscript{110}

Synonyms
Croderol; E422; glycerine; Glycon G-100; Kemstrene; Optim; Pricerine; 1,2,3-propanetriol; trihydroxypropane glycerol.

Chemical name
Propane-1,2,3-triol [56-81-5]

Description
Glycerine is a clear, colorless odorless, viscous, hydroscopic liquid. It has a sweet test, approximately 0.6 times as sweet as sucrose.

Functional categories
Antimicrobial preservative; emollient; humectant; plasticizer; solvent; sweetening agent; tonicity agent.

Solubility
Soluble in water, methanol and ethanol; slightly soluble in acetone; practically insoluble in benzene, chloroform and oils.

Viscosity

<table>
<thead>
<tr>
<th>Concentration of aqueous glycerin solution (% w/w)</th>
<th>Viscosity at 20\textdegree C (mPa s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>1.143</td>
</tr>
<tr>
<td>10</td>
<td>1.311</td>
</tr>
<tr>
<td>25</td>
<td>2.095</td>
</tr>
<tr>
<td>50</td>
<td>6.05</td>
</tr>
<tr>
<td>60</td>
<td>10.96</td>
</tr>
</tbody>
</table>
Stability and storage conditions
Mixture of glycerine with water, ethyl alcohol and propylene glycol is chemically stable. Preserve in a tight container to avoid moisture absorption.

Incompatibilities
Glycerin may explode if mixed with strong oxidizing agents such as chromium trioxide, potassium chlorate or potassium permanganate. In dilute solution, the reaction proceeds at a slower rate with several oxidation products being formed. Black discoloration of glycerin occurs in the presence of light or on contact with zinc oxide or basic bismuth nitrate. An iron contaminant in glycerin is responsible for the darkening in color of mixtures containing phenols, salicylates and tannin. Glycerin forms a boric acid complex, glyceroboric acid that is a stronger acid than boric acid.

Safety
Adverse effects are mainly due to the dehydrating properties of glycerin. When used as an excipient or food additive, glycerin is not usually associated with any adverse effects and is generally regarded as a nontoxic and nonirritant material.

Applications
Glycerin is used in a wide variety of pharmaceutical formulations including oral, otic, ophthalmic, topical and parenteral preparations

- In topical pharmaceutical formulations and cosmetics, glycerin is used primarily for its humectant and emollient properties.
- In parenteral formulations, glycerin is used mainly as a solvent.
- In oral solutions, glycerin is used as a solvent, sweetening agent, antimicrobial preservative and viscosity increasing agent. It is also used as a plasticizer and in film coatings. Glycerin is additionally used in topical formulations such as creams and emulsions.
- It is used as a plasticizer of gelatin in the production of soft gelatin capsules and gelatin suppositories.
- It is employed as a therapeutic agent in a variety of clinical applications, and is also used as a food additive.
### Table 3.12 Uses of glycerin

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial preservative</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Emollient</td>
<td>30</td>
</tr>
<tr>
<td>Humectant</td>
<td>30</td>
</tr>
<tr>
<td>Ophthalmic formulations</td>
<td>0.5–3.0</td>
</tr>
<tr>
<td>Plasticizer in tablet film coating</td>
<td>Variable</td>
</tr>
</tbody>
</table>

#### 3.4.3 Dibutyl Phthalate

**Synonyms**

Araldite 502; benzenedicarboxylic acid; benzene-o-dicarboxylic acid di-n-butyl ester; butyl phthalate; Celluflex DBP; DBP; dibutyl 1,2-benzenedicarboxylate; dibutyl benzene 1,2-dicarboxylate; dibutyl ester of 1,2-benzenedicarboxylic acid; dibutyl-o-phthalate; di-n-butyl phthalate; Elaol; Ergoplast FDB; Genoplast B; Hatcol DBP; Hexaplast M/B; Kodaflex DBP; Monocizer DBP; Palatinol C; phthalic acid dibutyl ester; Polycizer DBP; PX 104; RC Plasticizer DBP; Staflex DBP; Unimoll DB; Vestimol C; Witecizer 300.

**Chemical name:**

Dibutyl benzene-1, 2-dicarboxylate.

**Structural formula**

![Structural formula of Dibutyl Phthalate](image)

**Description**

Dibutyl phthalate occurs as an odorless, oily, colorless, or very slightly yellow colored, viscous liquid.
Functional category
Film former; plasticizer; solvent.

Solubility
Very soluble in acetone, benzene, ethanol (95%) and ether; soluble 1 in 2500 of water at 20°C.

Viscosity
Table 3.13 Dynamic viscosity of dibutyl phthalate at specified temperatures

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Dynamic viscosity (mPa s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>59</td>
</tr>
<tr>
<td>10</td>
<td>33</td>
</tr>
<tr>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>30</td>
<td>13</td>
</tr>
<tr>
<td>40</td>
<td>9</td>
</tr>
<tr>
<td>50</td>
<td>7</td>
</tr>
</tbody>
</table>

Stability and storage conditions
Dibutyl phthalate should be stored in a well closed container in a cool, dry, location. Containers may be hazardous when empty since they can contain product residues such as vapors and liquids.

Incompatibilities
Dibutyl phthalate reacts violently with chlorine. It also reacts with oxidizing agents, acids, bases and nitrates.

Safety
Dibutyl phthalate is generally regarded as a relatively nontoxic material, although it has occasionally been reported to cause hypersensitivity reactions. It is widely used in topical cosmetic and some oral pharmaceutical formulations.

Applications
- Dibutyl phthalate is used in pharmaceutical formulations as a plasticizer in film-coatings.
- It is also used extensively as a solvent particularly in cosmetic formulations such as antiperspirants, hair shampoos and hair sprays.
• In addition to a number of industrial applications, dibutyl phthalate is used as an insect repellent, although it is not as effective as dimethyl phthalate.