3.1 PRONIOSOMES

Vora B et al.\(^1\) have developed and extensively characterized both in-vitro and in-vivo proniosome based transdermal drug delivery system of levonorgestrel. On the basis of in-vitro observations the pronosomal formulation containing S 40:soya lecithin:cholesterol (4.5:4.5:1) and isopropanol was selected and patch having the area 0.63 cm\(^2\) (9 mm diameter) containing formulation equivalent to 1 mg drug was applied to the animals, in order to obtain the desired flux (20 mg/day). In-vivo study revealed that proniosomal gel bearing patch for levonorgestrel is overwhelmingly superior than levonorgestrel ointment at the same dose level.

Fang J et al.\(^2\) have investigated skin permeation of estradiol from various proniosome gel formulations across excised rat skin in-vitro. The EE and size of niosomal vesicles formed from proniosomes upon hydration were characterized. Proniosomes with S 40 and S 60 increased the permeation of estradiol across skin.

Alsarra IA et al.\(^3\) have investigated permeation of ketorolac across excised rabbit skin from various proniosome gel formulations using franz diffusion cells. Each of the prepared proniosomes significantly improved drug permeation and reduced the lag time. Proniosomes prepared with S 60 provided a higher ketorolac flux across the skin than did those prepared with T 20 (7- and 4-fold the control, respectively). A change in the cholesterol content did not affect the efficiency of the proniosomes, and the reduction in the lecithin content did not significantly decrease the flux.

Varshosaz J et al.\(^4\) have developed proniosomal gel for transdermal drug delivery of chlorpheniramine maleate based on S 40 and extensively characterized in-vitro. The results showed that lecithin produced more stable and larger vesicles with higher loading efficiency but lower dissolution efficiency than cholestrol and dicethyl phosphate. The ethanol produced larger vesicles (\(\approx 44 \mu m\)) and entrapped a greater amount of drug. The proniosomes that contained S 40/lecithin/ cholestrol prepared by ethanol showed optimum stability, loading efficiency (16.7%), particle size and release kinetic suitable for transdermal delivery of chlorpheniramine maleate.
Gupta A et al. have investigated the potential of proniosomes as a transdermal drug delivery system for captopril which was composed of various ratios of sorbitan fatty acid esters, cholesterol, lecithin prepared by coacervation-phase separation method. The method of proniosome loading resulted in an encapsulation yield of 66.7 - 78.7%. At refrigerated conditions, higher drug retention was observed.

Ibrahim MMA et al. have formulated and evaluated proniosomal transdermal carrier systems for flurbiprofen. Both S 40 and S 60 produced gel systems in presence or absence of cholesterol. Due to the skin permeation barrier, rabbit skin showed lower drug diffusion rates compared to cellophane membrane. The proniosomal composition controlled drug diffusion rates to be either faster or slower than the prepared flurbiprofen suspensions in HPMC gels or distilled water, respectively.

Chandra A et al. have investigated permeation of piroxicam from proniosome based reservoir type transdermal gel formulation across excised rat abdominal skin using keshery chein diffusion cell. It was observed that S 60 based formulations produced vesicles of smallest size and higher EE while those of S 80 produced vesicles of least EE. Incorporation of lecithin further enhanced EE. Maximum flux achieved was 35.61 µg/cm²/h, an enhancement was of 7.39 times as compared to control gel.

Azeem A et al. have formulated non-ionic surfactant vesicles of frusemide to enhance its skin permeation. With formulation containing S 40:soyalecithin: cholesterol (4.5:4.5:1), the plasma level in the rats had reached to a level of 0.42 ± 0.13 µg/ml at the sampling interval of 4 hr and remained within the therapeutic concentration range (1.66–0.3 µg/ml) for the next 12 hr.

Azarbayjani AF et al. have studied proniosomal formulations with non-ionic surfactant. Formulations with single surfactants were found to increase the skin permeation of haloperidol more than formulations containing two surfactants. The number of carbons in the alkyl chain of the non-ionic surfactant influenced the in-vitro permeation of haloperidol though the epidermis and the skin permeation was increased with increase in hydrophilic–lipophilic balance value of the surfactant.
Mahrous GM et al.\textsuperscript{10} have evaluated the potential of proniosomes as a carrier for transdermal delivery of meloxicam. Proniosomes prepared with S 60 provided a higher meloxicam flux (29.9µg/cm\textsuperscript{2}/h) across the rat skin than did those prepared with T 80 (22.30µg/cm\textsuperscript{2}/h). Testing of the anti-inflammatory effect of meloxicam proniosomal gel showed better pharmacological activity.

Alam MI et al.\textsuperscript{11} have developed low dose proniosomal gel containing celecoxib for the treatment of osteoarthritis. The entrapment was > 90%. The selected proniosomal gel (S 40: 1800 mg, cholesterol: 200 mg, soya lecithin: 900 mg) produced higher flux (0.17 mg/cm\textsuperscript{2}/h) and 100% inhibition of paw oedema in rats up to 8 h after carrageenan injection. It produced 95% and 92% inhibition after 12 h and 24 h, respectively.

El-Laithy HM et al.\textsuperscript{12} have designed a novel sustained release proniosomal system using sugar esters as non-ionic surfactants containing vinpocetine. All formulae exhibited high EE. Vesicle size analysis showed that all vesicles were in the range from 0.63 µm to 2.52 µm which favored efficient transdermal delivery. The extent of drug permeation was quite high (91%) after 48 h under occlusive conditions.

Ammar HO et al.\textsuperscript{13} have studied transdermal drug delivery of different proniosomal gel bases containing tenoxicam. The lecithin-free proniosomes prepared from T 20:cholesterol (9:1) proved to be stable with high entrapment and release efficiencies with flux of 0.11mg/cm\textsuperscript{2}/h. The investigated tenoxicam loaded proniosomal formula proved to be non-irritant, with significantly higher anti-inflammatory and analgesic effects compared to that of the oral market tenoxicam tablets.

Anindita D et al.\textsuperscript{14} have formulated and evaluated tretinoin proniosomal gel. The proniosome vesicles were of LUV type and spherical shape. The proniosome vesicles prepared with S 60, S 40 and cholesterol in formulation showed maximum EE (76.77±1.54%). The \textit{in-vitro} diffusion study carried out using sigma dialysis membrane showed sustained release pattern of tretinoin from proniosomal gel formulation. The comparative skin irritation study carried out on 18 healthy wistar rats of either sex showed remarkable decrease in signs of skin irritation caused by tretinoin.
3.2 IONTOPHORESIS

Delgado-Charro MB et al.\textsuperscript{15} have studied the effects of administered concentration and applied current density on the iontophoresis of nafarelin in-vitro. Nafarelin delivery did not increase linearly with applied concentration: while there is an increase when the donor concentration is doubled from 0.5 to 1.0 mg/ml, further increments in applied peptide level result in decreased transport.

Fang JY et al.\textsuperscript{16} have investigated the transdermal iontophoresis sodium nonivamide acetate. Iontophoresis increased the transdermal penetration flux of sodium nonivamide acetate as compared to the passive diffusion in this study. The iontophoretic flux of sodium nonivamide acetate increased following the decrease of donor buffer pH values. Comparing the various application modes, the discontinuous on/off cyclic current mode showed higher penetration capacity than did continuous mode which was due to the intensity of effective current which would not decay for on/off cyclic application of iontophoresis.

Tiwari SB et al.\textsuperscript{17} have investigated the potential for iontophoresis facilitated transdermal transport of ketorolac using rat skin. Increase in applied current density or decrease in ionic strength of the donor solution enhanced the flux of the drug. Continuous current was more potent than pulsed current in promoting ketorolac transdermal permeation. Increasing the frequency or on:off ratio of pulse current induced an enhancement of the flux through the skin. An increase in donor drug loading dose or increasing the duration of current application resulted in enhancement of the drug flux.

Al-Khalili M et al.\textsuperscript{18} have evaluated the effect of transdermal iontophoretic delivery of buspirone hydrochloride across hairless mouse skin. Increasing the current density from 0.05 to 0.1mA/cm\textsuperscript{2} resulted in doubling of the iontophoretic flux of buspirone hydrochloride, while increasing drug concentration from 1% to 2% had no effect on flux. Incorporating buspirone hydrochloride into ethanol:water (50:50 v/v) based gel formulations using carboxy methyl cellulose and hydroxypropyl methyl cellulose (HPMC) had no effect on iontophoretic delivery.
Hashim IIA et al.\textsuperscript{19} have evaluated the \textit{in-vitro} transdermal delivery of fluorescein isothiocyanate -NF-\(\kappa\)B decoy ODN using a pulse depolarization iontophoresis. The apparent flux values of FITC-NF-\(\kappa\)B decoy ODN were enhanced with increasing the current density and NF-\(\kappa\)B decoy ODN concentration by iontophoresis. Accumulation of fluorescein isothiocyanate -NF-\(\kappa\)B decoy ODN was observed at the epidermis and upper dermis by iontophoresis.

Sachdeva V et al.\textsuperscript{20} have investigated the use of iontophoresis for the delivery of terbinafine hydrochloride into hairless rat skin \textit{in-vivo}. Iontophoresis delivered significantly more drug into the deeper skin as compared to controls (p < 0.05). Drug levels in the SC and underlying skin increased with increasing duration of current application.

Calatayud-Pascual MA et al.\textsuperscript{21} have characterized the \textit{in-vitro} transdermal absorption of almotriptan through pig ear skin. Although both current densities applied produced a statistically significant increment with respect to passive permeation of almotriptan (p < 0.01), that of 0.50 mA/cm\(^2\) proved to be the best experimental condition for increasing the transport of almotriptan across the skin with increased the transdermal drug flux of 411-fold with respect to passive diffusion, reaching 264 ± 24 µg/cm\(^2\) h (mean ± SD). Based on these results, and taking into account the pharmacokinetics of almotriptan, therapeutic drug plasma levels for the management of migraine could be achieved via transdermal iontophoresis using a reasonably sized (around 7.2 cm\(^2\)) patch.

Djabri A et al.\textsuperscript{22} have examined the use of transdermal iontophoresis for the delivery of raniti-dine hydrochloride in children. In the presence of low levels of competing background electrolyte, ranitidine delivery increased linearly with applied current but was independent of the donor drug concentration. The second part of the study evaluated two Pluronic\textsuperscript{®} F-127 gels as potential vehicles for ranitidine delivery. Overall the results demonstrated that therapeutic paediatric doses of ranitidine (neonates: 0.09–0.17 µmol/kg h; 1 month to 12 years: 0.36–0.71 µmol/kg h) could be easily achieved by transdermal iontophoresis with simple gel patches of practical surface area (0.2–1.5 cm\(^2\)/kg).
3.3 COMBINED ENHANCEMENT APPROACHES

Sintov AC et al.\textsuperscript{23} have demonstrated the potential of the application of a short-term iontophoresis on the topical delivery of lidocaine hydrochloride from a microemulsion-based system. It was shown \textit{in-vitro} that by combining microemulsion application with a 10-min iontophoresis of 1.13 mA/cm\textsuperscript{2} electric current density, a significantly increased flux was obtained compared with a combination of aqueous drug solution with the same iontophoresis protocol. \textit{In-vivo} studies revealed that 57.71±18.65 and 18.43±9.17µg/cm\textsuperscript{2} were reached in the epidermis and dermis, respectively, at t = 30 min of microemulsion application, when iontophoresis was applied for 10 min.

Liu W et al.\textsuperscript{24} have investigated solid lipid nanoparticles hydrogel for transdermal iontophoretic drug delivery of triamcinolone acetonide acetate. Triamcinolone acetonide acetate - solid lipid nanoparticles gel possessed good stability, rheological properties, and high electric conductance. The enhancement of the cumulative penetration amount and the steady-state penetration flux of the penetrated drug were related to the particle size of triamcinolone acetonide acetate - solid lipid nanoparticles and the characteristics of the applied pulse electric current, such as density, frequency, and on/off interval ratio.

Manosroi A et al.\textsuperscript{25} have studied enhancement of transdermal absorption of luciferase plasmid by loading in elastic cationic liposomes and niosomes and the application of iontophoresis or the SC stripping method. All nanovesicles loaded with luciferase plasmid showed larger vesicular sizes than the nonloaded vesicles of about 1.4 times for liposomes and 1.7 times for niosomes. The fluxes in the receiving solution of luciferase plasmid loaded in nonelastic liposomes and niosomes with iontophoresis at 6 hours were 6.71 +/- 0.31 and 8.82 +/- 0.28 g/cm\textsuperscript{2}/h, respectively.

Jain S et al.\textsuperscript{26} have improved the bioavailability of isosorbide dinitrate through transdermal route by using cationic niosomal gel as a carrier with anodic iontophoresis. Isosorbide dinitrate -loaded cationic niosomes had an average diameter of 262±6.92 nm, polydispersity index of 0.217±0.02, zeta potential of +25.4±0.12, and EE of 68.16±1.14%. While free drug was found to degrade upon application of current,
interestingly, it was found that niosomes offered protection to isosorbide dinitrate from degradation during the iontophoresis. The in-vitro permeation studies with different current densities showed increase in transdermal flux and decrease in lag time by 11.15- and 2.42-fold (0.5 mA/cm$^2$), 12.66- and 2.58-fold (1.0 mA/cm$^2$), and 14.46- and 3.75-fold (1.5 mA/cm$^2$), respectively, as compared to passive diffusion of free drug.

Kajimoto K et al.\textsuperscript{27} have utilized charged liposomes as carriers, focused on a transfollicular route for delivery of the liposomes, and optimized iontophoretic conditions and lipid composition for this method in both in-vitro and in-vivo conditions. Authors identified the optimum condition (lipid composition: DOTAP/EPC/Chol = 2:2:1, current supply: 0.45mA/cm$^2$, duration: 1 h) for effective iontophoretic delivery of aqueous solution, which cannot be transferred into the skin without charged liposomes. Iontophoresis of liposomes encapsulating insulin onto a diabetes rat skin resulted in a gradual decrease in blood glucose levels, with levels reaching 20% of initial values at 18 h after administration. These lower blood glucose levels were maintained for up to 24 h.

Tomoda K et al.\textsuperscript{28} have loaded indomethacin and coumarin-6 in PLGA nanoparticles with an average diameter of 100 nm. Higher amount of indomethacin was delivered through skin when indomethacin was loaded in nanoparticles than indomethacin was free molecules. When iontophoresis was applied at 0.05mA/cm$^2$, permeability of indomethacin was much higher than that obtained by simple diffusion of nanoparticles through skin.

Silva SMC et al.\textsuperscript{29} have evaluated three nonionic ether-monohydroxyl surfactants (C12E1, C12E5, and C12E8) as skin permeation enhancers in the transdermal drug delivery of two drugs: ondansetron hydrochloride and diltiazem hydrochloride, formulated as hydrogels. Data obtained using diltiazem HCl showed that the use of the nonionic surfactant C12E5 resulted in higher enhancement ratios in passive studies, but C12E8 yielded slightly higher values of drug permeated (2678 µg/cm$^2$) than C12E5 (2530 µg/cm$^2$) when iontophoresis was also employed.
3.4 LITERATURE REVIEW ON NAPROXEN

Claramonte MDC et al.\textsuperscript{30} have studied the percutaneous absorption of naproxen from different gels, using a double-layer (hydrophilic/lipophilic) artificial membrane to determine the influence of the viscosity of the preparation and the thermodynamic activity of naproxen. The predominant factor appeared to be the activity of naproxen in the preparation, although viscosity seemed to affect the kinetics of the process.

Bonina FP et al.\textsuperscript{31} have synthesized and assayed I-Alkylazacycloalkan-2-one esters of naproxen to determine their stability in phosphate buffer and isopropyl myristate, susceptibility to undergoing \textit{in-vitro} enzymatic hydrolysis and flux through excised human skin. 1-ethylpyrrolidone and 1-ethylvalerolactam appear to be suitable promoieties for obtaining naproxen dermal prodrugs.

Valjakka-Koskela R et al.\textsuperscript{32} have investigated the skin penetration of naproxen from various phospholipid gel formulations through human cadaver skin in diffusion chambers. Presence of phospholipids decreased the skin penetration of naproxen from aqueous gels. The penetration enhancement effect of phospholipid with ethanol (more than 8% (m/v) ) was, however, more significant than that of phospholipid with propylene glycol.

Degim IT et al.\textsuperscript{33} have determined the permeation of naproxen through excised human skin and isolated perfused rabbit ear skin. Both Azone and capsaicin enhanced the permeation with an enhancement ratio of up to 4-fold in human and rabbit skin.

Rautio J et al.\textsuperscript{34} have synthesized and evaluated novel morpholinyl (4a) and piperazinylalkyl (4b-e) esters \textit{in-vitro} for their properties as bioreversible topically administered dermal prodrugs of naproxen. All of the prodrugs were app significantly more lipophilic (log P 50.7–3.9) than naproxen (log P 50.3). Among the prodrugs, two piperazinyl derivatives (4c and 4d) resulted in a 9- and 4-fold enhancement of permeation, respectively, when compared to naproxen itself at pH 7.4. 4c also resulted in a significantly (4-fold) better permeation than naproxen at pH 5.0.
Chapter 3

LITERATURE REVIEW

Attia DA et al.\textsuperscript{35} have formulated topical gel containing 1\% of naproxen sodium using various ratios of different type of gel forming agents as pectin, HPMC low and high viscosity, carboxymethyl cellulose, and carbopol 934 with and without penetration enhancers; isopropyl myristate and sodium lauryl sulphate. The PK parameters, were significantly (p <0.001) different following transdermal administration of 1\% naproxen sodium gel prepared with pectin without penetration enhancers compared with oral administration of reference naproxen sodium tablet NaprofenR.

Gupta V et al.\textsuperscript{36} have developed a transdermal gel formulation of naproxen, which would attenuate the GI related toxicities associated with oral administration. Naproxen gel formulations were made with carbopol 940 having tulsi oil (1 \%, 3 \%, 5 \%, and 7 \%) as penetration enhancer containing 2 \% of naproxen. Formulation containing naproxen (2 \%) and tulsi oil (5 \%) found to be better than other formulations.

Puglia C et al.\textsuperscript{37} have studied the percutaneous absorption of naproxen included in liposome formulations constituted of different lipids: SC lipids and phosphatidylcholine/cholesterol. Tape stripping corroborate the \textit{in-vitro} findings regarding SC lipids, suggesting that liposomes create a drug reservoir mixing with SC lipids, whilst phosphatidylcholine/cholesterol liposome promoted naproxen permeation through the skin.

Barakat NS et al.\textsuperscript{38} have studied the effect of glycofurol vehicle-based gel, in the topical penetration of naproxen. Three gelling and adhesive agents were examined: Carbopol 974P, Gantrez AN 119, and polyvinylpyrrolidone K30. A significant increase in permeability parameters was observed in optimized formulation containing 2\% Transcutol as a permeation enhancer.

Okura NU et al.\textsuperscript{39} have evaluated the potential application of microemulsions as a transdermal drug delivery for naproxen. The higher permeation rates and lower paw oedema (after 6 hr - 0.71 ± 0.46\%) were found with formulation (isopropyl myristate, Labrafil M, Cremophor EL, isopropyl alcohol and 0.5 N sodium hydroxide) than the commercial gel formulation.
Argemi A et al.⁴⁰ have prepared and characterized transdermal patches impregnated with naproxen. A mixture of ethylene vinyl acetate and Eudragit R E100 (80:20, w/w) is used as a polymeric matrix to obtain a thin membrane to be impregnated. Results have shown that a sustained delivery for more than 24 h is obtained.

Tiana Q et al.⁴¹ have investigated microemulsion with high content of naproxen for transdermal delivery. Naproxen microemulsions composed of 4% isopropyl myristate, 18% T 80, 18% ethanol and water were prepared. The using of phase inversion temperature method resulted in the maximum content of naproxen in microemulsion increased from 1.98±0.13% to 4.12±0.07%, accordingly the permeation rate of naproxen through excised mice skin increased from 135.13±5.50 to 214.46±7.53 g cm⁻² h⁻¹.

Harsoliya MS et al.⁴² have developed transdermal drug delivery system of naproxen drug with chitosan polymer for treatment of arthritis. All the formulations showed drug content in the range of 86.45-94.63% indicating uniform distribution of drug throughout the base. The % moisture content of all the formulations was found to be in the range 2.31 – 6.0 %. The folding endurance of all the formulations was found in the range of 0.40 - 0.47.

Moghimipour E et al.⁴³ have formulated and characterized a microemulsion systems as a topical delivery system of naproxen. Formulations prepared by mixing of appropriate amount of surfactant including T 80 and S 80, co-surfactant such as propylene glycol and oil phase including Labrafac PG – transcutol P (10:1 ratio). The mean droplets size was in the range of 7.03 to 79.8 nm, and its refractory index and pH were 1.45 and 6.75, respectively. Viscosity range was 253.73-802.63cps. Drug release profile showed that 26.15% of the drug released in the first 24 hours of experiment.

Mishra S et al.⁴⁴ have formulated a modified proniosomal gel of naproxen by coacervation phase separation technique based on nonionic surfactants (S 40, S 60) and cholesterol. 3² factorial design of experiments was used to optimize the various formulation variables. This formulation of proniosomes is a practical and simple method for the immediate preparation of niosomal for transdermal delivery of Naproxen.
Chapter 3

LITERATURE REVIEW

3.5 LITERATURE REVIEW ON LORNOXICAM

Kavitha K et al.\textsuperscript{45} have developed and evaluated matrix-type transdermal therapeutic system containing lornoxicam. The formulation, F1 (HPMC E5 alone) showed maximum release of 95.76 ± 1.38 % in 8 h, where as F2 (Ethyl cellulose alone) showed maximum release of 58.64 ± 1.14 % in 24 h. The formulation, F3 with combination of polymers (1:1) showed maximum release of 76.76 ± 2.1 % in 24 h.

Stationwala R et al.\textsuperscript{46} have formulated pluronic lecithin organogel of lornoxicam and evaluated its suitability for topical application. Ten formulations were developed using lornoxicam, Pluronic F-127, lecithin, isopropyl myristate, water, sorbic acid and potassium sorbate. Formulation, containing 3% lecithin and 20% pluronic is an effective formulation for transdermal delivery of lornoxicam as it showed satisfactory pH, viscosity, spreadability, drug content and high % cumulative percent drug release (which is 90.13 %).

Xi H et al.\textsuperscript{47} have investigated the skin enhancement mechanism of ion pairs for lornoxicam with organic amines from the standpoint of ion-pair stability. Various organic amines, triethylamine, diethylamine, N-(20-hydroxyethanol)-piperdine, diethanolamine and triethanolamine, were employed as the counter ions for enhancing lornoxicam across the rabbit skin \textit{in-vitro}. All the amines, especially triethylamine, provided an obvious enhancing effect for lornoxicam. The results demonstrated that the stability of ion-pair complexes was closely related with the basicity of organic amines and exhibited a great contribution on skin permeation of lornoxicam.

Kapil S et al.\textsuperscript{48} have projected nonionic surfactant vesicles having lornoxicam with different Spans. The \textit{in-vitro} permeation profile of optimized formulation was compared with that of Lornoxicam solution. Superior CAP/cm\(^2\) (8.57) was observed in S 60(1:1) niosomes.

Baviskar DT et al.\textsuperscript{49} have prepared matrix-type transdermal drug delivery system of lornoxicam. Transdermal patches of lornoxicam were designed with ethyl
cellulose:polyvinylpyrrolidone and Eudragit RL 100:Eudragit RS 100 in different ratios with propylene glycol as plasticizer (5%) and T 80 as permeation enhancer using the solvent evaporation technique. Formulations A3 and B3 exhibited greatest (311.04 µg and 306.32 µg, respectively) cumulative amount of drug release. The Higuchi model seemed to be the most appropriate model describing release kinetics from all patches ($r^2 = 0.9847-0.9971$). Formulations A3 and B3 were found to enhance the bioavailability of lornoxicam by 3.1 and 2.7 times, respectively, with reference to the oral dosage form.

Nabarawi MAE et al.\textsuperscript{50} have evaluated the lornoxicam transdermal patches through \textit{in-vitro} skin permeation, skin irritation and biological evaluation on rat induced paw edema. There was very good correlation between lornoxicam flux and the presence of isopropyl myristate, oleic as well as propylene glycol compared to other oils and triacetine. Span80 had significantly improved lornoxicam permeation from eudragit blends (E100). while combining transcutol- castor oil showed no remarkable increase in drug flux. The primary irritancy index proved the non-irritancy of the drug or any of the film components and showed that the innovated films are safe to be applied to skin for the intended period of time. Lornoxicam patches had significantly inhibited the carrageenan induced rat paw edema compared to oral treatment.

Shahzad Y et al.\textsuperscript{51} have formulated and optimized lornoxicam containing topically applied lotions to deliver it transdermally. The best fit quadratic model revealed that low level of HPMC and intermediate level of EG in the formulation was optimum for enhancing the drug flux across silicone membrane. The drug flux from the optimized lotion across rabbit skin was significantly better that that from the control formulation. Use of Box–Wilson statistical design successfully elaborated the influence of formulation variables on permeation of lornoxicam form topical formulations, thus, helped in optimization of the lotion formulation.

3.6 LITERATURE REVIEW ON TRAMADOL

Shinde AJ et al.\textsuperscript{52} have designed to develop suitable transdermal matrix patches of tramadol hydrochloride, using HPMC, Eudragit RL-100 and Eudragit RS-100 with
triethyl citrate as a plasticizer and dimethyl sulfoxide as a penetration enhancer. Different batches developed using Eudragit RL-100 : HPMC and Eudragit RS-100 : HPMC in ratio of 2 : 8, 4 : 6, 6 : 4, and 8 : 2. Physical evaluation was performed such as moisture content, moisture uptake, tensile strength, flatness, and folding endurance. The batch containing Eudragit RL-100 : HPMC (8 : 2) showed 79.65% release within 12 h and batch containing Eudragit RL-100 : HPMC (2 : 8) showed only 58.30% release in 12 h.

Chandak AR et al.\textsuperscript{53} have designed and developed a matrix dispersion type transdermal delivery system of tramadol using different concentrations and polymeric grades of hydroxypropyl methylcellulose (HPMC K4M, K15M & K100M). Films were evaluated for their physicochemical characteristics, followed by \textit{in-vitro} and \textit{in-vivo} evaluation. The drug release followed Higuchi kinetics ($r = 0.979–998; P < 0.001$). Percent of drug dissolved at a given time versus plasma drug concentration correlated statistically.

Takasuga S et al.\textsuperscript{54} have investigated the feasibility of transdermal delivery of tramadol, by anodal iontophoresis using Ag/AgCl electrodes was \textit{in-vitro} and \textit{in-vivo}. The in-vitro steady-state skin permeation flux of tramadol currentdependently increased without significant differences among the three different skin types (porcine ear skin, guinea-pig abdominal skin and hairless mouse abdominal skin). In the \textit{in-vivo} pharmacokinetic study, plasma concentrations of tramadol steadily increased and reached steady state (336 ng/ml) 3 h after initiation of current supply, and the \textit{in-vivo} steady-state transdermal absorption rate was 499 mg/cm\textsuperscript{2} per h as calculated by a constrained numeric deconvolution method.

Phatak AA et al.\textsuperscript{55} have developed and optimized a stable nonionic surfactant vesicular system known as niosomes for Tramadol HCl. The formulations were evaluated for entrapment efficiency (39.34 - 88.26\%), particle size (0.33±0.15µm to 0.99±0.17µm), zeta potential, viscosity and in-vitro drug release (56.71% to 101.91%) in 12 hrs. The in-vitro permeability of the drug was evaluated by using dialysis membrane. The results of the \textit{in-vitro} drug release / permeability in 12 hrs shows better release in comparison with pure drug and marketed formulation.
3.7 DRUG PROFILE
3.7.1 NAPROXEN

Name: Naproxen
Description: Naproxen is a propionic acid derivative related to the arylacetic acid group of nonsteroidal anti-inflammatory drugs.
Structure: 

\[ \text{IUPAC Name: } (+)-(S)-2-(6-methoxynaphthalen-2-yl) propanoic acid \]
Mole. weight: 230.26
BCS: II
Formula: \( \text{C}_{14}\text{H}_{14}\text{O}_{3} \)
Melting point: 153°C
Solubility: 15.9 mg/L (at 25 °C), soluble in chloroform, alcohol, sparingly soluble in ether, practically insoluble in water
Log P 3.18
pKa 4.15
Brand Names: Aleve, Naprelan, Naprosyn, Anaprox, Apronax
Indication: For the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, tendinitis, bursitis, and acute gout.
Pharmacodynamics: Naproxen is a member of the arylacetic acid group of NSAIDs. Naproxen has analgesic and antipyretic properties. As with other NSAIDs, its ability to inhibit prostaglandin synthesis may be involved in the anti-inflammatory effect.
Mechanisms of action: The mechanism of action is same as other NSAIDs, is believed to be associated with the inhibition of cyclooxygenase activity. Two unique cyclooxygenases have been described in mammals. The constitutive cyclooxygenase, COX-1, synthesizes prostaglandins necessary for normal GI and renal function.
Absorption: Naproxen itself is rapidly and completely absorbed from the GI tract.
with an in-vivo bioavailability of 95%. Food causes a slight decrease in the rate absorption.

Bioavailability: 95% (oral)

Protein binding: 99%

Distribution: Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels Naproxen is greater than 99% albumin-bound. At doses of Naproxen greater than 500 mg/day there is less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses.

Metabolism: Naproxen is extensively metabolized in the liver to 6-0-desmethyl Naproxen, and both parent and metabolites do not induce metabolizing enzymes.

Excretion: The clearance of Naproxen is 0.13 mL/min/kg. Approximately 95% of the Naproxen from any dose is excreted in the urine, primarily as Naproxen (<1%), 6-0-desmethyl Naproxen (<1%) or their conjugates (66% to 92%). The plasma half-life of the Naproxen anion in humans ranges from 12 to 17 hours.

Half-life: 12-24 hours

Medical Use: Naproxen is commonly used for the reduction of pain, fever, inflammation, and stiffness caused by conditions including migraine, osteoarthritis and primary dysmenorrhea.

Adverse effects: COX-2 selective and nonselective NSAIDs have been linked to increases in the number of serious and potentially fatal cardiovascular events, such as myocardial infarctions and strokes.

Dosage froms: Suppository – rectal; Suspension, Tablet coated, Tablet (ER) – oral

Stability: Stable under normal conditions, Temperatures above 40° C (104°F) should be avoided.
3.7.2 LORNOXICAM

Name: Lornoxicam

Description: Lornoxicam (chlortenoxicam) is a new NSAID of the oxicam class with analgesic, anti-inflammatory and antipyretic properties.

Structure: 

Mole. weight: 371.8192 g/mol

BCS: II

Formula: C_{13}H_{10}ClN_{3}O_{4}S_{2}

IUPAC Name: (3E)-6-chloro-3-[hydroxy(pyridin-2-ylamino)methylene]-2-methyl-2,3-dihydro-4H-thieno[2,3-e][1,2]thiazin-4-one 1,1-dioxide

Melting point: 225-230 °C

Solubility (at 25 °C): Soluble in water (<1 mg/ml), methanol (sparingly), DMSO (2 mg/ml), DMF, and ethanol (<1 mg/ml)

Log P: 2.53

PKa: Strong acidic – 6.88; strong basic – 4.78

Brand names: Lorcam, Xefon,

Indication: For the treatment of acute mild to moderate pain, as well as pain and inflammation of the joints caused by rheumatic diseases.

Pharmacodynamics: Lornoxicam is a potent inhibitor of the cyclooxygenase enzymes, which are responsible for catalyzing the formation of prostaglandins and thromboxane from arachidonic acid. Lornoxicam's inhibition of cyclooxygenase does not lead to an increase in leukotriene formation, meaning that arachidonic acid is not moved to the 5-lipoxygenase cascade, resulting in the minimization of the risk of adverse events.

Mechanisms of action: Like other NSAIDS, lornoxicam's anti-inflammatory and analgesic activity is related to its inhibitory action on prostaglandin and thromboxane synthesis through the inhibition of both COX-I & II.

Absorption: Lornoxicam is absorbed rapidly and almost completely from the GIT.
Bioavailability: 90-100%

Protein binding: Lornoxicam is 99% bound to plasma proteins

Metabolism: Lornoxicam is metabolized completely by cyp 2C9 with the principal metabolite being 5’-hydroxy-lornoxicam and only negligible amounts of intact lornoxicam are excreted unchanged in the urine. Approximately 2/3 of the drug is eliminated via the liver and 1/3 via the kidneys in the active form.

Half life: 3-5 hours

Elimination: 2/3 hepatic, 1/3 renal

Medical Use: Lornoxicam is used for the treatment of various types of pain, especially resulting from inflammatory diseases of the joints, osteoarthritis, surgery, sciatica, and other inflammations

Adverse effects: Side effects similar to other NSAIDs, most commonly mild ones like GI disorders (nausea and diarrhea) and headache.

Dosage forms: Injection (4mg/ml) – Intravenous route, Table (4mg, 8mg) - Oral route

Stability: Highly unstable in solution showing rapid oxidation and hydrolytic cleavage, leading to the formation of a large number of degradation products within weeks, on standing at room temperature. The stability for injection in 0.9% sodium chloride injection prepared according to clinical regime showed that no significant change in 72 h.

3.7.3 TRAMADOL HCl

Name: Tramadol

Description: A narcotic analgesic proposed for moderate to severe pain. It may be habituating.

Structure:

![Tramadol Structure](image)
Mole. weight: 263.4 g/mol
BCS: I
Formula: C₁₆H₂₅NO₂
IUPAC Name: 2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol
Melting point: 180-181˚C
Solubility: Freely soluble in methanol, ethanol, slightly soluble in acetone
Log P: 2.4
pKa: 9.41
Brand names: ConZip, Durela, Ralivia, Rybix, Ryzolt, Tramal, Tridural, Ultram,
Indication: Indicated in the treatment of moderate to severe pain. Consider for those prone to constipation or respiratory depression. Tramadol is used to treat postoperative, dental, cancer, and acute musculoskeletal pain and as an adjuvant to NSAID therapy in patients with osteoarthritis.

Pharmacodynamics:
Two complementary mechanisms appear applicable: binding of parent and M1 metabolite to µ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to µ-opioid receptors.

Mechanisms of action:
Tramadol and its O-desmethyl metabolite (M1) are selective, weak OP3-receptor agonists. Opiate receptors are coupled with G-protein receptors and function as both positive and negative regulators of synaptic transmission via G-proteins that activate effector proteins. As the effector system is adenylate cyclase and cAMP located at the inner surface of the plasma membrane, opioids decrease intracellular cAMP by inhibiting adenylate cyclase. Subsequently, the release of nociceptive neurotransmitters is inhibited. The analgesic properties can be attributed to norepinephrine and serotonin reuptake blockade in the CNS, which inhibits pain transmission in the spinal cord.

Absorption:
Racemic tramadol is rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability of a 100 mg
oral dose is approximately 75%. The mean peak plasma concentration of racemic tramadol and M1 occurs at two and three hours, respectively, after administration in healthy adults.

**Bioavailability:** 70-75% (oral), 77% (rectal), 100% (IM)

**Protein binding:** 20%

**Metabolism:** Hepatic. The major metabolic pathways appear to be N- and O-demethylation and glucuronidation or sulfation in the liver. One metabolite (O-desmethyltramadol, denoted M1) is pharmacologically active in animal models. CYP3A4 and CYP2B6 facilitates the biotransformation of tramadol to N-desmethyl-tramadol. CYP2D6 facilitates the biotransformation of tramadol to O-desmethyl-tramadol.

**Half life:** 6.3 ± 1.4 hr

**Elimination:** Urine (95%)

**Medical Use:** Tramadol is used primarily to treat moderate-severe pain, both acute and chronic. Tramadol is recommended for the management of pain in fibromyalgia by the European League Against Rheumatism. Its analgesic effects take about one hour to come into effect and 2–4 hours to peak after oral administration with an immediate-release formulation. On a dose-by-dose basis tramadol has about one-tenth the potency of morphine and is approximately equally potent when compared to pethidine and codeine.

**Adverse effects:** The most common adverse effects of tramadol include nausea, dizziness, dry mouth, indigestion, abdominal pain, vertigo, vomiting, constipation, drowsiness and headache. Compared to other opioids respiratory depression and constipation is considered less of a problem with tramadol.

**Dosage forms:** Capsule – 100mg, 150mg, 200mg, 300mg  
Tablet – 50 mg, Tablet (ER) – 100mg, 200mg, 300mg  
Tablet (orally disintegrating) – 50 mg; Injections – 50-100 mg/ml

**Stability:** Stable under normal conditions of use.
3.8 EXCIPIENT PROFILE^59

3.8.1 SORBITAN ESTER (SORBITAN FATTY ACID ESTERS)

Synonyms, chemical name, formula and molecular weight:

<table>
<thead>
<tr>
<th>Name</th>
<th>Synonym</th>
<th>Chemical Name</th>
<th>Formula</th>
<th>Mol. Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorbitan monolaurate</td>
<td>S 20</td>
<td>Sorbitan monododecanoate</td>
<td>C18H34O6</td>
<td>346</td>
</tr>
<tr>
<td>Sorbitan monopalmitate</td>
<td>S 40</td>
<td>Sorbitan monohexadecanoate</td>
<td>C22H42O6</td>
<td>403</td>
</tr>
<tr>
<td>Sorbitan monostearate</td>
<td>S 60</td>
<td>Sorbitan monooctadecanoate</td>
<td>C24H46O6</td>
<td>431</td>
</tr>
<tr>
<td>Sorbitan monooleate</td>
<td>S 80</td>
<td>(Z)-Sorbitan mono-9-octadecenoate</td>
<td>C24H44O6</td>
<td>429orb</td>
</tr>
</tbody>
</table>

Structural Formula:

\[
\text{R1 = R2 = OH, R3 = R where R = (C11H23)COO for laurate, (C17H33)COO for oleate, (C15H31)COO for palmitate, (C17H35)COO for stearate}
\]

**Functional Category:** Emulsifying agent; nonionic surfactant; solubilizing agent; wetting and dispersing / suspending agent.

**Applications in Pharmaceutical Formulation or Technology:** Sorbitan esters are widely used in cosmetics, food products, and pharmaceutical formulations as lipophilic nonionic surfactants. They are mainly used in pharmaceutical formulations as emulsifying agents in the preparation of creams, emulsions, and ointments for topical application. When used alone, sorbitan esters produce stable water-in-oil emulsions and microemulsions but are frequently used in combination with varying proportions of a polysorbate to produce water-in-oil or oil-in-water emulsions or creams of varying consistencies.

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emulsifying agent, Solubilizing agent, Wetting agent</td>
<td>-</td>
</tr>
</tbody>
</table>
Chapter 3

LITERATURE REVIEW

Used alone in water-in-oil emulsions 1-15 %
Used in with hydrophilic emulsifiers in oil-in-water emulsions 1-10 %
Used to increase the water-holding properties of ointments 1-10 %
For poorly soluble, active constituents in lipophilic bases 1-10 %
For insoluble, active constituents in lipophilic bases 0.1-3

Description: Sorbitan esters occur as cream- to amber-colored liquids or solids with a distinctive odor and taste.

<table>
<thead>
<tr>
<th>Name</th>
<th>Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorbitan monolaurate</td>
<td>Yellow viscous liquid</td>
</tr>
<tr>
<td>Sorbitan monopalmitate</td>
<td>Cream solid</td>
</tr>
<tr>
<td>Sorbitan monostearate</td>
<td>Cream solid</td>
</tr>
<tr>
<td>Sorbitan monooleate</td>
<td>Yellow viscous liquid</td>
</tr>
</tbody>
</table>

Typical Properties:

<table>
<thead>
<tr>
<th>Name</th>
<th>Acid Value</th>
<th>Density (gm/cm$^3$)</th>
<th>HLB Value</th>
<th>Hydroxyl value</th>
<th>Iodine number</th>
<th>Melting point(˚C)</th>
<th>Pour point(˚C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorbitan monolaurate</td>
<td>7</td>
<td>1.01</td>
<td>8.6</td>
<td>159-169</td>
<td>7</td>
<td>---</td>
<td>16-20</td>
</tr>
<tr>
<td>Sorbitan monopalmitate</td>
<td>3-7</td>
<td>1.0</td>
<td>6.7</td>
<td>270-303</td>
<td>1</td>
<td>43-48</td>
<td>---</td>
</tr>
<tr>
<td>Sorbitan monostearate</td>
<td>5-10</td>
<td>---</td>
<td>4.7</td>
<td>235-260</td>
<td>---</td>
<td>53-57</td>
<td>---</td>
</tr>
<tr>
<td>Sorbitan monooleate</td>
<td>8</td>
<td>1.01</td>
<td>4.3</td>
<td>193-209</td>
<td>---</td>
<td>---</td>
<td>12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name</th>
<th>Saponification value</th>
<th>Surface tension (mN/m)</th>
<th>Viscosity (mPa s)</th>
<th>Water content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorbitan monolaurate</td>
<td>159-169</td>
<td>28</td>
<td>3900-4900</td>
<td>0.5</td>
</tr>
<tr>
<td>Sorbitan monopalmitate</td>
<td>142-152</td>
<td>36</td>
<td>Solid</td>
<td>1</td>
</tr>
<tr>
<td>Sorbitan monostearate</td>
<td>147-157</td>
<td>46</td>
<td>Solid</td>
<td>1</td>
</tr>
<tr>
<td>Sorbitan monooleate</td>
<td>149-160</td>
<td>30</td>
<td>970-1080</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Stability and Storage Conditions: Gradual soap formation occurs with strong acids or bases; sorbitan esters are stable in weak acids or bases. Sorbitan esters should be stored in a well-closed container in a cool, dry place.

Ph. D. Thesis
Safety: Sorbitan esters are widely used in cosmetics, food products, and oral and topical pharmaceutical formulations and are generally regarded as nontoxic and nonirritant materials. However, there have been occasional reports of hypersensitive skin reactions following the topical application of products containing sorbitan esters. When heated to decomposition, the sorbitan esters emit acrid smoke and irritating fumes.

Handling Precautions: Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

3.8.2 POLYOXYETHYLENE SORBITAN FATTY ACID ESTERS

Synonyms: Polysorbate 20 – T 20; Polysorbate 40 – T 40; Polysorbate 60 – T 60; Polysorbate 80 – T 80

Chemical Names:

<table>
<thead>
<tr>
<th>Polysorbate</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysorbate 20</td>
<td>Polyoxyethylene 20 sorbitan monolaurate</td>
</tr>
<tr>
<td>Polysorbate 40</td>
<td>Polyoxyethylene 20 sorbitan monopalmitate</td>
</tr>
<tr>
<td>Polysorbate 60</td>
<td>Polyoxyethylene 20 sorbitan monostearate</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>Polyoxyethylene 20 sorbitan monooleate</td>
</tr>
</tbody>
</table>

Empirical Formula and Molecular Weight:

<table>
<thead>
<tr>
<th>Polysorbate</th>
<th>Formula</th>
<th>Molecular weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysorbate 20</td>
<td>C58H114O26</td>
<td>1128</td>
</tr>
<tr>
<td>Polysorbate 40</td>
<td>C62H122O26</td>
<td>1284</td>
</tr>
<tr>
<td>Polysorbate 60</td>
<td>C64H126O26</td>
<td>1312</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>C64H124O26</td>
<td>1310</td>
</tr>
</tbody>
</table>

Structural Formula:

\[ w + x + y + z = 20 \] (Polysorbate 20, 40, 60 & 80); R = fatty acid
Functional Category: Emulsifying agent; nonionic surfactant; solubilizing agent; wetting, dispersing/suspending agent.

Applications in Pharmaceutical Formulation or Technology: Polysorbates containing 20 units of oxyethylene are hydrophilic nonionic surfactants that are used widely as emulsifying agents in the preparation of stable oil-in-water pharmaceutical emulsions. They may also be used as solubilizing agents for a variety of substances including essential oils and oil-soluble vitamins, and as wetting agents in the formulation of oral and parenteral suspensions.

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emulsifying agent, Solubilizing agent, Wetting agent</td>
<td>-</td>
</tr>
<tr>
<td>Used alone in oil-in-water emulsions</td>
<td>1-15 %</td>
</tr>
<tr>
<td>Used with hydrophilic emulsifiers in oil-in-water emulsions</td>
<td>1-10 %</td>
</tr>
<tr>
<td>Used to increase the water-holding properties of ointments</td>
<td>1-10 %</td>
</tr>
<tr>
<td>For poorly soluble active constituents in lipophilic bases</td>
<td>1-10 %</td>
</tr>
<tr>
<td>For insoluble active constituents in lipophilic bases</td>
<td>0.1-3 %</td>
</tr>
</tbody>
</table>

Description: Polysorbates have a characteristic odor and a warm, somewhat bitter taste. They are yellow oily liquid at 25°C.

Typical Properties:

<table>
<thead>
<tr>
<th>Polysorbate</th>
<th>Acid value (%)</th>
<th>Hydroxyl value</th>
<th>Saponification value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysorbate 20</td>
<td>2.0</td>
<td>96-108</td>
<td>40-50</td>
</tr>
<tr>
<td>Polysorbate 40</td>
<td>2.0</td>
<td>90-105</td>
<td>41-52</td>
</tr>
<tr>
<td>Polysorbate 60</td>
<td>2.0</td>
<td>81-96</td>
<td>45-55</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>2.0</td>
<td>65-80</td>
<td>45-55</td>
</tr>
</tbody>
</table>

Acidity/alkalinity: pH = 6.0–8.0 for a 5% w/v aqueous solution.

Flash point: 149°C

<table>
<thead>
<tr>
<th>Polysorbate</th>
<th>HLB value</th>
<th>Specific gravity at 25°C</th>
<th>Viscosity (mPa s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysorbate 20</td>
<td>16.7</td>
<td>1.1</td>
<td>400</td>
</tr>
<tr>
<td>Polysorbate 40</td>
<td>15.6</td>
<td>1.08</td>
<td>500</td>
</tr>
<tr>
<td>Polysorbate 60</td>
<td>14.9</td>
<td>1.1</td>
<td>600</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>15.0</td>
<td>1.08</td>
<td>425</td>
</tr>
</tbody>
</table>

Solubility: Polysorbate—soluble in ethanol and water and insoluble in oil.
Stability and storage conditions: Polysorbates are stable to electrolytes and weak acids and bases; gradual saponification occurs with strong acids and bases. Also, in common with other polyoxyethylene surfactants, prolonged storage can lead to the formation of peroxides. Polysorbates should be stored in a well-closed container, protected from light, in a cool, dry place.

Incompatibilities: Discoloration and/or precipitation occur with various substances, especially phenols, tannins, tars, and tarlike materials.

Safety: There have, however, been occasional reports of hypersensitivity to polysorbates following their topical and intramuscular use. Polysorbates have also been associated with serious adverse effects, including some deaths, in low-birthweight infants intravenously administered a vitamin E preparation containing a mixture of polysorbates 20 and 80. When heated to decomposition, the polysorbates emit acrid smoke and irritating fumes.

Handling Precautions: Eye protection and gloves are recommended.

3.8.3 CHOLESTEROL

Synonyms: Cholesterin; cholesterolum.

Chemical Name: Cholest-5-en-3β-ol

Empirical Formula and Molecular Weight: C_{27}H_{46}O 386.67

Structural Formula:

Functional Category: Emollient; emulsifying agent.

Applications in Pharmaceutical Formulation or Technology: Cholesterol is used in cosmetics and topical pharmaceutical formulations at concentrations of 0.3–5.0% w/w as an emulsifying agent. It imparts water-absorbing power to an ointment and has emollient activity. Cholesterol also has a physiological role.
Description: Cholesterol occurs as white or faintly yellow, almost odorless, pearly leaflets, needles, powder, or granules. On prolonged exposure to light and air, cholesterol acquires a yellow to tan color.

Typical Properties:
- Boiling point: 360°C
- Density: 1.052 g/cm$^3$ for anhydrous form
- Dielectric constant $D^{20}$: 5.41
- Melting point: 147-150°C
- Solubility at 20°C: soluble in acetone, 1 in 7 in benzene, 1 in 4.5 in chloroform, 1 in 78 in ethanol, 1 in 2.8 ether, practically insoluble in water

Stability and Storage Conditions: Cholesterol is stable and should be stored in a well-closed container, protected from light.

Incompatibilities: Cholesterol is precipitated by digitonin.

Safety: Cholesterol is generally regarded as an essentially nontoxic and nonirritant material at the levels employed as an excipient.

3.8.4 LECITHIN

Synonyms: E322; egg lecithin; LSC 5050; LSC 6040; mixed soybean phosphatides; ovolecithin; soybean lecithin; soybean phospholipids; Stermpur; vegetable Lecithin.

Chemical Name: Lecithin

Structural Formula:

![Structural Formula of Lecithin]

R1 and R2 are fatty acids, which may be different or identical.

Functional Category: Emollient; emulsifying agent; solubilizing agent.

Applications in Pharmaceutical Formulation or Technology: Lecithins are mainly used in pharmaceutical products as dispersing, emulsifying, and stabilizing agents and are included in intramuscular and intravenous injections, parenteral nutrition formulations, and topical products such as creams and ointments. Liposomes in which lecithin is
included as a component of the bilayer have been used to encapsulate drug substances; their potential as novel delivery systems has been investigated.

**Description:** Lecithins vary greatly in their physical form, from viscous semiliquids to powders. They may also vary in color from brown to light yellow, depending upon whether they are bleached or unbleached or on the degree of purity.

**Typical Properties:**
- **Density:** 0.97 g/cm$^3$ for liquid lecithin; 0.5 g/cm$^3$ for powdered lecithin.
- **Iodine number:** 95–100 for liquid lecithin; 82–88 for powdered lecithin.
- **Saponification value:** 196
- **Solubility:** Lecithins are soluble in aliphatic and aromatic hydrocarbons. They are practically insoluble in cold vegetable and animal oils, polar solvents, and water. When mixed with water, however, lecithins hydrate to form emulsions.
- **Stability and Storage Conditions:** Lecithins decompose at extreme pH. They are also hygroscopic and subject to microbial degradation. When heated, lecithins oxidize, darken, and decompose. All lecithin grades should be stored in well-closed containers protected from light and oxidation.
- **Incompatibilities:** Incompatible with esterases owing to hydrolysis.
- **Safety:** Lecithin is a component of cell membranes and is therefore consumed as a normal part of the diet. When used in topical formulations, lecithin is generally regarded as a nonirritant and nonsensitizing material.

**HPMC**
- **Synonyms:** Cellulose hydroxypropyl methyl ether, methyl hydroxypropylcellulose
- **Chemical Name:** Cellulose, 2-Hydroxypropyl methyl ether
- **CAS Registry Number:** 9004-65-3
- **Molecular weight:** 10,000 – 15,000,000
- **Structural formula:**

![Structural formula of HPMC](image-url)
**Functional category:** Coating agent, film-former, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.

**Application:** In oral products, HPMC is primarily used as a tablet binder, in film-coating and as an extended release tablet matrix. It is used as a suspending and thickening agent in topical formulations, particularly in ophthalmic preparations.

**Description:** HPMC is an odorless and tasteless, white or creamy-white colored fibrous or granular powder.

**Stability and storage conditions:** HPMC powder is a stable material although it is hygroscopic after drying. Solutions are stable between pH 3-11. It undergoes a reversible sol to gel transformation upon heating and cooling respectively. HPMC powder should be stored in a well-closed container, in a cool, dry place.

**Incompatibilities:** HPMC is incompatible with some oxidizing agents

**Safety:** HPMC is generally regarded as a nontoxic and nonirritant material although excessive oral consumption may have a laxative effect.

**REFERENCES**


