# Chapter 2: Review Literature

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2.1 Diclofenac Sodium (DS):

Chemical structure

![Chemical structure of Diclofenac Sodium](image)

2.1.1 Description: It is a Non Steroidal Anti-Inflammatory agent (NSAID) with analgesic and antipyretic activity. It is mainly available as sodium and potassium salt.

- **Brand names**: Apo-iclo, Allvoran, Assaren, Delphimix, Benfofen.
- **Chemical name**: Sodium [2[(2,6dichlorophenyl)amino]phenyl] acetate
- **Molecular weight**: 318.13 g/mol
- **Molecular formula**: C_{14}H_{10}Cl_{2}NNaO_{2}
- **Categories**: Cyclooxygenase (COX) inhibitor. Non Steroidal Anti-Inflammatory Drug (NSAID).
- **CAS number**: 15307-86-5.
- **Colour**: Off white crystalline solid.
- **Odour**: Odourless.
- **Dissociation constant (pK_{a})**: 4.0±0.2 at 25°C in water.
- **pH**: Between 7.0 & 8.5 in a solution (1 in 100).
Melting point  : 283-285 °C.
Water solubility  : 2.37 mg /ml.
Log P  : 4.51.
Pka  : 4.15.

Dosage Ophthalmic (0.1 % w/v)

Adult:

Ocular inflammation (Postoperative): 1 drop 4 times in a day, beginning one day following cataract surgery and extending up to 2 weeks after surgery. In few cases, treatment has been continued for 6 weeks or even longer period.

Inhibition of intra operative miosis: 1-2 drops 4 times per day for 3 days before surgery. 1-2 drops every ¼ hr for 4 doses 1 hr prior to surgery. 1 drop every ¼ hr after surgery and continuing 4 times daily starting 4-6 hrs after surgery for 3 days.

Corneal ulcers: A drop to the injured eye 4-5 times in a day.

Keratoconjunctivitis: 1 drop to the affected eye 4-5 times a day.

Conjunctivitis: 1 drop to the affected eye 4-5 times a day.

2.1.2 Pharmacokinetics

Ocular: Results from a BA study divulged that plasma levels of DS following ocular administration of 2 drops to each eye was less than 10 ng/mL over a 4 hrs period.

Oral:

Absorption: It is totally absorbed (100 %) following enteric administration when compared to intravenous administration, measured by urine recovery method. However, because of its extensive first-pass metabolism only about 50% of the administered drug is available systemically. Food does not have significant effect on
the diclofenac absorption. But, there is usually a lag in absorption onset (1 to 4.5 hrs) and a reduction in the $C_{\text{max}}$ (20%).

**Distribution:** It is distributed throughout the body into many body tissues and fluids. Protein binding of DS is approximately 99%. The mean Vd of diclofenac is 1.34 l/kg.

**Metabolism and Excretion:** It is eliminated predominantly as its 4-hydroxy metabolite. Its exact metabolism is not totally elucidated till date, but it is swiftly and extensively metabolized in the liver. It undergoes extensive hydroxylation and conjugation reaction with glucorinic acid, taurine amide, sulphuric acid and other biological ligands. Following oral or IV administration of DS in healthy subjects, approximately about 50-70% of dose is excreted in urine and about 30-35% through feces within 96 hrs of administration.

**Clearance:** Oral clearance-622 ml/min

Renal clearance-less than 1ml/min

2.1.3 **Mechanism of action:** Its anti-inflammatory action is due to inhibition of cylooxygenase (COX-1 and COX-2) enzyme and leukocyte migration, leading to the peripheral inhibition of prostaglandins (PG) synthesis. Its analgesic activity is mainly due to inhibition of PG synthesis and whereas antipyretic effect is due to action on the hypothalamus, which causes peripheral vessels dilation, increased blood flow to skin and subsequent heat dissipation.

2.1.4 **Side effects:**
   - **Systemic:** Upset of stomach, heartburn, nausea, diarrohea, headache, drowsiness dizziness and constipation may occur.
   - **Ocular:** Following adverse drug events were reported in roughly ≤10% of the patients: acute increased IOP, abnormal vision, blurred vision, corneal deposits, conjunctivitis, corneal edema, corneal opacity, corneal lesion, eyelid inflammation, eye pain, redness, iritis, itching, irritation, ocular allergy and lacrimation disorder.

2.1.5 **Drug Interactions:** Concomitant uses of acetyl salicylic acid and NSAIDs increase the risk of serious gastro intestinal events, hence patients taking DS must be advised not take aspirin. NSAIDs may increase the hypoglycemic activity of oral hypoglycemics or insulin because PGs are directly involved in the regulatory
mechanism of glucose metabolism and probable due to displacement of oral hypoglycemic from plasma protein.

**Munish Ahuja et al.**, studied the effect of different formulation factors on permeation of DS, some experimental and marketed eye drops across excised cornea of goat. Their study revealed that apparent permeability of drug reduces on raising the concentration of drug from 0.05 to 0.15 (% w/v) or pH of the dosage form from 6.0 to 8.0 or adjusting the isotonicity with mannitol or adding viscolizing agents to the formulation. Presence of sodium metabisulfite or disodium edetate (EDTA) or combination of parabens (methyl and propyl parabens) in formulation favored permeation of DS [79].

**Reer O et al.**, studied the effect of cyclodextrin derivatives on diclofenac *in vitro* permeability across excised pig cornea. In their study they used different degree substitution of (Hydroxypropyl)-beta-cyclodextrin (HP beta CD) and two amorphous methylated cyclodextrins. Significant decrease in DS hemolytic activity was observed by adding HP beta CD and they proposed a solution containing HP beta CD buffered in the pH range 6.5 to 7 as a useful ocular formulation [80].

**Desai et al.**, claimed in their patent, a stable formulation of DS, an acidic drug can be formulated by using $\alpha$-tocopheryl polyethylene glycol succinate (E-TPGS) as solubilizer and preserved by using benzalkonium chloride. In their study the Vitamin E-TPGS is used as solubilizer, could decrease discomfort of eyes in aqueous conditions. The caffeine which was added to reduce ocular discomfort, surprisingly shown synergistic with Vitamin E-TPGS to reduce discomfort and it also potentiated the preservative efficacy of bezalkonium chloride [81].

**Ahuja M et al.**, reported maximum *in vitro* corneal permeation across excised goat cornea for diclofenac (0.2 %w/v) in sesame oil than any other oil used in their study and they reported addition of preservative (Benzyl alcohol) increased drug permeability could be due increased partitioning of drug in to aqueous phase [82].

**Quintana-Hauet al.**, formulated a novel carrier sophisen and its derivatives for ocular delivery. In their study they mixed DS and Cyclosporine-A with Sophisen to provide two new ophthalmic solutions, 3A Ofteno TM and Modusik-A Ofteno TM,
respectively. In their study it was concluded that Sophisen is a better carrier for ocular delivery of DS [83].

Cooper et al., formulated drug loaded nanoparticles; their findings revealed that, DS loaded PLGA based NPs could be prepared by simple evaporation-diffusion technique with little concentrations of PVA and idodecyl dimethyl ammonium bromide (DMAB) stabilizers utilizing ethyl acetate as organic solvent. Drug loaded NPs developed in their study provided adequate diclofenac entrapment levels and showed superior levels of stability with a remarkable decrease in overall particle size [84].

Cetin et al., prepared DS nanoparticles by using combination of PLGA (Biodegradable polymer) and Eudragit® L100 (Non-Biodegradable polymer). Their study revealed that the encapsulation efficiency and the release behavior of drug were greatly altered by the amount of Eudragit in the blend [85].

Agnihotri et al., prepared DS nanoparticle suspension by emulsion and solvent evaporation technique from PLGA and poly(lactic-co-glycolic-acid)-leucine [poly[Lac(Glc-Leu)]] polymers and reported nanoparticle suspension was devoid of any irritant effect on cornea, iris, and conjunctiva for as long as 24 hrs after application on rabbit eye. Thus proved NPs are suitable inert carrier for ocular delivery [86].

Ahuja et al., prepared DS loaded Eudragit S-100 based nano-suspensions by nanoprecipitation and reported nano-suspensions were stable with average particle size of 172 nm, polydispersibility index of 0.14, zeta potential of -23.7±/-6.07 mV and nanosuspended particles were spherical in shape [87].

Attamma et al., prepared SLNs with a blend of homolipid (goat fat) and phospholipid, and evaluated for ocular delivery of DS using bio-engineered human cornea made from stromal fibroblasts, immortalized human corneal endothelial cells and epithelial cells CEPI 17 CL 4. Their study showed high drug encapsulation efficiency, sustained release of diclofenac and enhanced permeation through the bio-engineered cornea [88].

Asasutjarit et al., studied the outcome of formulation compositions on size and zeta potential of DS loaded NPs prepared using biodegradable polymer chitosan. The nanoparticles consisting of chitosan, drug and tripolyphosphate at4:1:1ratio; were prepared at pH 5.0, 5.5 and 6.0. In their study it was found that, nano sized particles
prepared at pH 5.0 and 6.0 were turbid due to precipitation of drug and chitosan, respectively and it was found that the ratio of 4:1 for chitosan: drug at pH 5.5 provided drug-loaded NPs possessing particle size in the range of nanometer with positive surface charge and concentration of Tween 80 and tripolyphosphate also affected size of particles, zeta potential and stability of drug-loaded nano sized particles [89].

2.2 Ketorolac tromethamine (KT):
Brand names: Toradol, Acular, Acalr LS, Acuvail, Sprix.
Molecular weight: 376.4 g/mol

![Chemical structure of Ketorolac tromethamine](image)

Chemical name: 2-amino-2-(hydroxymethyl)propane-1,3diol;5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid.

Molecular formula: C_{19}H_{24}N_{2}O_{6}.

Categories: COX inhibitors, NSAID.

CAS number: 74103-07-4.

Colour: A crystalline solid.

Odour: Odourless.

Melting point: 165-167 °C.

Dissociation constant (pK\(_a\)): 3.84.

pH: Between 6.5-7.8.

Water solubility: 25 mg /ml.

Log p: 2.66.

Half Life: 2.5 hrs for the S-enantiomer and 5 hrs for the R-enantiomer
Dosage (Ophthalmic):

**Pediatric Patients:**

**Conjunctivitis:** Children <3 years of age: 1 drop of 0.5% w/v solution in to diseased eye 4 times/day.

**Postoperative Ocular Inflammation:** Children < 3 years of age: 1 drop of 0.5% w/v solution to the eye prior to surgery, 1 drop 4 times/day starting 24 hrs after surgery and continuing instillation for 2 weeks after surgery.

**Postoperative Ocular Pain:** Children < 3 years of age, who underwent ocular incisional refractive surgery: 1 drop of 0.5% w/v (preservative-free) solution 4 time/day to the eye that undergone surgery as required for up to 3 days after surgery. Children more than 3 years of age go through corneal refractive surgery: 1 drop (200 µg) of a 0.4% solution 4 times/day to the eye that underwent surgery as required for up to 4 days after surgery.

**Adults:**

**Conjunctivitis:** One drop of 0.5% solution 4 times/ day.

**Postoperative Ocular Inflammation:** 1 drop of 0.5% w/v solution in the eye undergoing surgery 4 times/day beginning 24 hrs after surgery and continuing up to 2 weeks after surgery.

**Postoperative Ocular Pain:** Patients going through ocular incisional refractive surgery: 1 drop of a 0.5% w/v (preservative-free) solution 4 times/day to the affected eye continuing instillation up to 3 days after surgery. Patients who will go through corneal refractive surgery: 1 drop of a 0.4% w/v solution 4 times/day continuing instillation up to 4 days after surgery.

**Postoperative Cystoid Macular Edema:** 1 to 2 drops of 0.5% w/v solution in the eye undergoing surgery every 6–8 hrs beginning 24 hrs prior to surgery and continuing instillation for 3–4 weeks next surgery.

**Chronic Aphakic or pseudophakic Cystoid Macular Edema:** 1–2 drops of a 0.5%w/v solution 4 times in a day for 2–3 months.

**Cautions:**

**Contraindications:** Known ketorolac hypersensitivity or any ingredient/ingredients’ in the dosage form.
Warnings/Precautions: Hematologic Effects: It may extend the bleeding time by inhibiting platelet aggregation.

Cross-sensitivity: Possible cross-sensitivity with acetyl salicylic acid, phenyl acetic acid derivatives, and other NSAIDs. Use carefully in individuals with history of hypersensitivity to these agents.

Ocular Effects: Its continuous use may cause keratitis. In susceptible individuals, prolonged use may cause epithelial breakdown, erosion, corneal thinning, ulceration or perforation, which may be seriously sight-threatening. If symptoms of corneal epithelial breakdown occur, its instillation should be terminated immediately and close monitoring corneal health is necessary. Increased hazard of detrimental corneal effects and sight-threatening, in those patients who underwent complicated ocular surgeries, corneal epithelial defects, diabetes mellitus, dry eye syndrome, rheumatoid arthritis, or repeated ocular surgeries within a short duration; caution to taken in such cases.

Pregnancy: Category C. As for as possible its use in the third trimester should be avoided, due to probable premature closure of ductus arteriosus.

Absorption:

Bioavailability: Its ocular and systemic absorption is not totally elucidated; however, trace amount was observed systemically following ocular instillation when compared to oral or parenteral doses. Very less amount of plasma concentration (10.7–22.5 ng/mL) of KT was detectable following its topical application.

Distribution: Distribution into human ocular tissues and fluids not fully evaluated till date. Ketorolac crosses the placental barrier and distributed into milk following systemic administration.

Plasma Protein Binding: More than 99 %.

Sandoval et al., conducted a study between 0.4 % and 0.5 %w/v KT ophthalmic solutions to correlate the effectiveness and ocular tolerance following routine phacoemulsification and lens implantation. Their study revealed that 0.4% KT ophthalmic solution is as effective as 0.5% in reducing inflammation and patients
reported less eye irritation, mainly burning and stinging with 0.4 % ophthalmic solution [90].

**Gu L. et al.**, studied the thermal reactivity of KT in aqueous buffered solutions (pH-1.1 to 12.4) at 60°C to 100°C and concluded that, distribution of the four products formed pH dependent and KT is unstable undergoing both acid and base catalyzed degradation [91].

**Malhotra et al.**, Studied *in vitro* corneal permeation across excised goat cornea of KT ophthalmic solution (0.5 % w/v) having equimolar (0.02 M) amount of phosphate (pH 6.5 and 7), citrate (pH 6.5), borate (pH 7) and citrate-phosphate (pH 7) buffers. % Cumulative permeation was more with PO₄ buffered drops at pH 6.5. They also investigated the outcome of pH and ionic strength on permeation of KT from buffered (phosphate) drops. In their study, it was revealed that unbuffered drug formulation at pH 6.5-8.5 showed maximum chemical stability; considering chemical stability and corneal permeation un-buffered KT ophthalmic solution (pH 6.5) was considered optimal for ocular delivery [92].

**Malhotra et al.**, studied the outcome of additives such as preservatives, antioxidants and viscolizing agents on ketorolac transcorneal permeation at different pH of aqueous drops of drug across excised goat and rabbit cornea. Their study showed maximum permeation of KT from formulation containing preservative (Benzalkoniumchloride) and EDTA across goat cornea and thiomersal decreases KT permeation [93].

**Malhotra et al.**, formulated ocular drops using oil as carrier and ophthalmic ointments of Ketorolac acid and KT. They studied the *in vitro* transcorneal permeation using goat cornea. Maximum cumulative (%) permeation of KT was found for 0.2% w/v in sesame oil succeeded by corn and soyabean oil drops which is due to corneal hydration. Addition of benzyl alcohol to oil drops reduces Ketorolac acid permeation and corneal hydration indicating possible protective effect of benzyl alcohol against corneal damage. Permeation studies on ointments having either ketorolac acid or KT salt sowed better permeation than formulation containing KT aqueous solution. Their study concluded that for better trans-corneal permeation, ketorolac 0.2% (w/v) drops formulated using sesame oil, containing 0.5% v/v benzyl
alcohol and ocular ointment containing 0.5% (w/w) KT in solubilized state appear suitable for ocular administration[94].

**Gupta et al.**, formulated polymeric micelles of KT from copolymer of N-isopropyl acrylamide, vinyl pyrrolidone and acrylic acid with cross-linkage with \(N,N'\)-methylene bis-acrylamide. Their study revealed that, two fold increases in ketorolac ocular availability was due to increased residence time and mucoadhesiveness of NP with no damage to cornea as compared to ketorolac suspension. Pharmacodynamic evaluation of NP formulation in PG-E2 induced ocular inflammation in rabbits showed a higher ocular anti-inflammatory activity for 5 hrs compared with the ketorolac aqueous suspension [95].

**Paliwal et al.**, tried to improve bioavailability of KT by entrapping it in polymeric vehicle. They used different polymers like HPMC, Na CMC, Eudragit type E/RL/RS, Carbopol 934 and Carbopol ETD 2020 National Formulary to formulate KT. They found increased ocular availability with carbopol, which could be due to mucoadhesion [96].

**Asik et al.**, formulated KT loaded chitosan NP for ocular delivery by using co-precipitation technique and successfully entrapped 34, 36 and 41 % for 0.8, 1.6 and 3.2 mg initial KT amount sequentially [97].

**Basu et al.**, successfully formulated KT loaded microspheres by using complex coacervation and simple coacervation without using cross linking agents to avoid possible side effects associated with cross linking agents [98].

**Yasmin Begum et al.**, described the entrapment of KT in liposome vesicles composed of Dipalmitoyl phosphatidyl choline and Distearoyl phosphatidyl choline (DSPC) with optimum quantity of cholesterol. Formulated liposomal samples were spherical in shape and exhibited concentric lamellae. Thus they successfully prepared reproducible liposome’s of ketorolac with good stability and appreciable controlled drug release [99] with an intention to lessen the disadvantages associated with traditional ocular drops.

**Jaya raja Kumar and Selvadurai Muralidharan.**, successfully formulated KT loaded Microparticle Gel by preparing microparticles by emulsion solvent diffusion technique and then dispersing the gelling agent in appropriate amount of microparticles [100].
2.3 Polymer Profile:

Poly-ε-caprolactone (PCL) [101]:

**Description:** Poly-ε-caprolactone is a biodegradable polymer; it is non-toxic, broadly miscible, mechanical compatibility with many polymers and good adhesion to broad spectrum substrates.

**Trade names:** Insta morph, Friendly plastic, Shape lock, Polymorph, Protoplasm

**State:** Solid.

**Color:** Colourless crystalline solid.

**Temperature:** Glass transition temperature 60°C.

**Stability:** Thermal and hydrolytic stability.

**Chemical structure:**

![Chemical structure of PCL](image)

**Chemical name:** (1,7)-polyoxepan-2-one.

**Synonyms:** 2-oxepanone homopolymer.

6-caprolactone polymer.

**Chemical formula:** \((\text{C}_6\text{H}_{10}\text{O}_2)\text{n}\).

**Molecular weight:** 40,000 g mol\(^{-1}\).

**CAS no:** 24980-41-4.

**Melting point:** 60°C.

**Uses:** The polymer can be widely used as a plasticizer and release agent to improve their processing performance. PCL is degraded by hydrolysis of its ester linkage in physiological conditions and approved by FDA, hence received a great attention in pharmaceutical field to use as bio-implantable biomaterial.

**Solubility:**

- Insoluble in: Water.
- Soluble in: Aromatic solvents and chlorinated hydrocarbons.
**Handling:** Avoid heating the product above the decomposition temperature.

**Storage:**
- Keep in original packing, closed.
- In a dry area.
- Keep away from ignition and heat sources.

*Z. Zili et al.*, prepared griseofulvin loaded PCL nanosized spheres and capsules by nanoprecipitation. Nanosized particles formulated showed high encapsulation efficiency with mean particle size of about 250–326 nm and 390–400 nm for spheres and capsules respectively. In their study it was concluded that, higher dissolution rate of nanosized particles should enhance the BA of drug and possibly its efficiency to treat dermatomycosis when compared to micronized griseofulvin [102].

*F. Lince et al.*, prepared PCL nanoparticles by a turbulent precipitation through solvent displacement. Two different molecular weights of PCL were used to prepare NP using acetone (Solvent) and water (Co solvent). Important kinetic and thermodynamic parameters, like interfacial tension and solubility of PCL in water–acetone mixtures were determined and the impact of process parameters on the particle size distribution was investigated. Results clearly showed the influence of mixing on the particle size distribution and how mixing should be monitored in order to get a nanoparticle formulation with particular characteristics [103].

*H. H. Joo et al.*, developed hinokitiol loaded nanocapsules by adopting emulsion diffusion method. PCL was utilized as rate controlling material and the core material was hinokitiol solution (dissolved in octyl salicylate). Three different kinds of emulsifying agents were used in emulsification, namely cetyl trimethyl ammonium chloride (CTAC), SLS, gelatin. Nanocapsules formulated using CTAC or SLS were hundreds of nanometers in size and the surface potential was greater than 20 mV. Where as in the case the nano sized capsules formulated with the mixture of CTAC and gelatin the value was between 0 -20 mV. Stable nanocapsules in pH range of 3-11 were obtained when formulated by using either CTAC or SLS. While the nanocapsules formulated using the mixture of CTAC and gelatin, were not stable in size in same pH range. *In vitro* results showed increased permeation of drug. Especially nanocapsules formulated using SLC were prominent in promoting the
permeation which could be due to SLS influence as a permeation enhancer. But in confocal laser it was observed that the nanocapsules themselves hardly penetrated into hairless mouse skin [104].

**J. I. Lee et al.,** fabricated temperature-responsive microspheres for releasing the protein in response to change in surrounding temperature. PCL–Pluronic, a polymer which is sensitive to temperature was synthesized into block copolymers with two different chain lengths of PCL. Proteins loaded microparticles were formulated by a W/O/W emulsion method. SEM images of microspheres showed microparticles had porous structures due to hydrophilic nature of Pluronic blocks. After 7 days of incubation at 37°C, temperature-response release of protein from particles was monitored with changing temperature between 20 and 37°C. Protein release rate was less when the micro spheres were incubated at 20 °C and the release rate recovered at 37°C, confirming temperature responsive release rate. The length of PCL blocks attached to Pluronic was mainly responsible to control the release rate [105].

**E Bilensoy et al.,** prepared nanoparticles using chitosan (CS), PCL coated with CS (CS-PCL) and PCL coated with poly-l-lysine (PLL-PCL) to encapsulate Mitomycin C (MMC). The main aim of the research was to prolong the residence time of nanoparticles thereby increasing local drug concentration and to prevent drug loss during bladder discharge. NP size varied between 180 and 340 nm, depending on type of polymer used for preparation and coating. Positive surface charge on particles was due to cationic polymer chitosan. Encapsulation efficiency of MMC depended on hydrophilic nature of the polymer used, because MMC is water-soluble. A 2-fold and 3-fold increase in encapsulation for CS-PCL and PLL-PCL nanoparticles respectively; was due to a hydrophilic coat on particles. In complete drug release was observed in case CS and PLL-PCL particles due to strong polymer–drug interactions. CS-PCL nanoparticles were found to be promising in delivery of MMC with respect to anticancer efficacy tested against MB49 bladder carcinoma cell line [106].

**C. L. Peng et al.,** synthesized and characterized amphiphilic four armed star shaped chlorine core diblock copolymers based on methoxy poly (ethylene glycol) (mPEG) and PCL. This amphiphilic star block copolymer can be used in a photodynamic therapy functionalized drug delivery system. In their research they successfully loaded paclitaxel, a hydrophobic drug in inner hydrophobic core of micelles. After
drug loading the particle size was increased from 71 to 103 nm. Surprisingly, these micelles were found to improve the cytotoxicity of paclitaxel significantly in MCF-7 cells after irradiation through a synergistic effect evaluated by median effect analysis. That functionalized micellar delivery system was a potential dual carrier for the synergistic combination of photodynamic therapy and chemotherapy for the treatment of cancer [107].

Marchal-Heussler et al., incorporated carteolol in PCL nanoparticles and nano sized capsules to enhance the ocular absorption of this anti glaucomatous drug. The polymer used in their experimental study was PCL. They tested the prepared dosages forms for IOP on intraocular hypertensive-induced rabbits and concluded that decrease in IOP was very much pronounced with carteolol entrapped in the colloidal carriers than commercial available eye drops. Further, NC displayed a better therapeutic effect than NP, which was due to ready availability of drug in NC for partitioning [108].

Ranjita misra et al., incorporated more than 70 % of doxycycline in PLGA: PCL nanoparticles by altering the formulations variables such as polymer ratio, amount of drug loading (w/w), electrolyte addition, solvent selection and pH in the preparation [109].

Zhaoliang Zhang et al., increased the solubility of rapamycin by $10^3$ times as compared with native rapamycin by incorporating this drug in nano-formulation using poly($\varepsilon$-caprolactone)-poly(ethylene glycol)-poly($\varepsilon$-caprolactone) (PCEC) NP by an emulsion evaporation method [110].

Clavo et al., evaluated nanocapsules having an oily core (Migliol 840) surrounded by a PECL coat, as a potential vehicles for the topical ocular administration of cyclosporin A. Their results showed 5 times high corneal level for drug loaded NP as compared to oily drops of cyclosporine [111].

Calvo et al., studied the mechanism of interactions of PCL with cornea by using confocal laser scanning microscope. Their study revealed that PCL nanocapsules were penetrated corneal epithelial cells by endocytosis and these results suggest the capability of PCL colloidal carriers to specifically target drugs to the cornea while avoiding systemic loss of drug through the conjunctiva [112].
2.4 Solvent Profile:

2.4.1 Ethyl Acetate [113]:

Nonproprietary Names:  
BP: Ethyl acetate  
Ph Eur: Ethylis acetas  
USPNF: Ethyl acetate

Synonyms:  
Acetic acid ethyl ester; acetic ester; acetic ether; acetoxyethane; aethylium acetas; ethyl ethanoate; vinegar naphtha.

Chemical Name:  
Ethyl acetate.

Empirical Formula:  
C₄H₈O₂.

Molecular Weight:  
88.1 g/mol.

Structural Formula: 
![Structural Formula](image)

Functional Category:  
Flavoring agent; solvent.

Description:  
Ethyl acetate is a clear, colorless, volatile liquid with a pleasant fruity, fragrant and slightly acetous odor, and has a pleasant taste when diluted. Ethyl acetate is flammable.

Boiling point:  
76.5-77.5°C.

Dielectric constant:  
6.11.

Density:  
0.902 g/cm³ at 20°C.

CAS Number:  
141-78-6.

Viscosity:  
0.423 at 25 °C.

Partition coefficient:  
Log P (octanol/water) = 0.7.

Refractive index:  
\( n^\circ_20 = 1.3719 \).

Solubility:  
Soluble 1 in 10 of water at 25°C; ethyl acetate solubility in water is more at lower temperature than the higher temperature. It is completely miscible with acetone, chloroform, dichloromethane, ethanol (95%), ether and with most other organic liquids.
Applications:

- In pharmaceutical preparations, ethyl acetate is primarily used as a solvent, although it has also been used as a flavoring agent.
- It is included in topical solutions, gels, and in edible printing inks used for tablets as a solvent.
- Ethyl acetate increases the solubility of chlorthalidone and modifies the polymorphic crystal forms of piroxicam pivalate and mefenamic acid. It also used in the formulation of microspheres and as a chemical enhancer for the transdermal iontophoresis of insulin.

Incompatibilities: Ethyl acetate reacts vigorously with strong oxidizing agents, strong alkalis, strong acids and nitrates to cause fires or explosions. It also reacts vigorously with chlorosulfonic acid, lithium aluminum hydride, 2-chloromethylfuran, and potassium tert-butoxide.

Safety: It is used in foods, oral and topical pharmaceutical formulations. It is relatively nontoxic and nonirritant excipient material. However, it can irritate mucous membranes and at high concentrations it may cause CNS depression. Over exposure symptoms include irritation of the eyes, nose, and throat, narcosis, and dermatitis. It has not been shown to be a human carcinogen or a reproductive or developmental toxin.

Handling Precautions: Follow normal precautions appropriate to the circumstances and quantity of material handled. Wearing of gloves and eye protection is recommended. In the United Kingdom, the occupational exposure limit for ethyl acetate is 400 ppm (short-term) and 200 ppm (long-term).

Stability and Storage Conditions: It should be stored in an airtight container, protected from direct sunlight light and at a temperature ☐ 30°C. It is slowly decomposed by moisture and becomes acidic; the material can absorb up to 3.3% w/w water. Ethyl acetate decomposes on heating to produce ethanol and acetic acid, and will emit acrid smoke and irritating fumes.

2.4.2 Dichloromethane [113, 114]

Synonyms: Methylene chloride, Solmethine, Methylene dichloride, Narkotil, Solaesthin, Di-clo, Freon 30.

Chemical Name: Methylene dichloride.
Empirical Formula : \( \text{CH}_2\text{Cl}_2 \).

Molecular Weight : 84.93 g/mol.

Functional Category : Solvent.

Description : This is a colourless, volatile liquid with a moderately sweet aroma.

Structural Formula:

![Structural Formula]

CAS Number: 75-09-2.

Boiling point: 39.8-40°C.

Dielectric constant: 8.93 at 25°C.

Density: 1.3266 g/cm³, liquid at 20°C.

Partition coefficient: 5.65.

Refractive index: 1.4242.

Solubility: Sparingly soluble in water and completely miscible with ethanol (96 %).

Applications:

- Because of its volatile nature and capacity to dissolve in a wide range of organic compounds, it is used as solvent for many chemical processes.
- It is used to strip paint and as a degreaser. In the food industry it is used to decaffeinate tea and coffee as well as to prepare extracts of hops and other flavorings. Due to its volatility, in aerosols it is used as propellant and in polyurethane foams as a blowing agent.
- It chemically welds certain plastics, for example, it is used to close the casing of electric meters.
- Also used in the garment printing industry for removal of heat-sealed garment transfers.

Incompatibilities: It is incompatible with aluminium, alkali metals, strong caustics, strong oxidizers, some forms of plastic and titanium.
**Safety:** Although it is the least toxic of the simple chlorohydro carbons, its high volatility makes it an acute inhalation hazard. It is metabolized in the liver to carbon monoxide possible leading to carbon monoxide poisoning. Acute exposure by inhalation may cause optic neuropathy and hepatitis. Prolonged skin contact can lead to skin irritation or burns.

**Handling Precautions:** Follow normal precautions relevant to the circumstances and quantity of organic material handled. Eye protection and gloves are recommended. Maintain good ventilation.

**Stability and Storage Conditions:** It is stable under ordinary storage conditions and use. It should be stored in an air-tight containers made of plain, galvanized, or lead-lined, mild steel, or glass.

DK Sahana *et al.*, used different solvents in NP preparation in order to optimize the formulation in terms of size of particle, entrapment and release behavior using estradiol as a model drug. In their study they adapted emulsion diffusion evaporation method for NP preparation using DMAB or PVA as stabilizers. They used the following solvents either alone or in combination; Acetone (ACE), chloroform, Ethyl acetate (EA) and dichloromethane (DCM). When DMAB was used, smaller particles were observed as compared to PVA regardless of the solvents and combinations used. When PVA was used as a stabilizer particles with higher entrapment were produced when a combination of solvents was used. Higher entrapment was observed when EA in combination with DCM was used with both stabilizers. Nearly uniform *in vitro* release pattern was observed irrespective of the stabilizers used. *In situ* uptake studies showed better uptake with smaller particles. *In vivo* bioavailability of optimized formulation was assessed in male Sprague Dawley rats at a dose of 1 mg/rat. *In vivo* studies reveled that particle size has significant role in determining the fate of nanoparticles [115].

K. C. Song *et al.*, prepared PLGA nanoparticles by an emulsion diffusion method. To assess the influence of organic phase on the particle sizes of nanoparticles, different organic solvents like EA, propylene carbonate, ACE and DCM were used in the study with several stabilizers (DMAB, PVA and Pluronic F-68). With DMAB small sized PLGA nanoparticles with size range below 70 nm were obtained for EA and poly carbonate, due to their partially water miscibility; while larger nanoparticles of size
range \( \square \) 290 nm were obtained for ACE and DCM as a fully water miscible and a water immiscible solvent, respectively. However, with PVA or Pluronic F-68, a big difference in average particle sizes between solvents was not observed and all nano sized particles showed a large diameter above 110 nm, regardless of the type of organic phase [116].

**L Peltonen et al.**, developed a new method, modified nanoprecipitation for the formulation of poly-(l)-lactide nanoparticles. The main aim of their study was to assess the influence of co-solvent on the particles morphology, size, encapsulation efficiency, degree of crystallinity, x-ray diffraction (XRD) reflection pattern and surface charge of the particles. In their study they used low-molecular-weight (2000 g/mol) poly-(l)-lactide as a polymer and sodium cromoglycate as a drug. ACE, ethanol, and methanol were selected as co-solvents for their study. When compared to acetone and methanol, optimal NP and high formation efficiency particles were achieved with ethanol. The particles prepared using ethanol and acetone were appeared smooth and round in shape, while with methanol particles were irregular in shape. Decrease in particles size was observed with decreasing inner organic phase volume with all the solvents, but the particles were more prone to aggregate. The XRD reflection pattern and the degree of crystallinity were more dependent on the volume of inner phase than on the properties of the individual co-solvents. Negative zeta potential values of all formulations explain the increased tendency toward particle aggregation [117].

**M Trotta et al.**, investigated the usefulness of slightly water-miscible solvents like triacetin, butyl lactate and benzyl alcohol to prepare drug nanosuspensions by a solvent quenching technique using Mitotane as a model drug. They prepared NP by emulsifying a drug containing organic phase in an aqueous phase containing a stabilizer followed by swift displacement of the organic solvent from the internal to the external aqueous phase, provoking nanosized particles formation. To verify the influence of droplet size emulsion on the particle size, 0.1 or 0.2% of different emulsifiers (Tween 80, caprylyl-capryl glucoside or lecithin) and different homogenization conditions were used. At high pressure homogenization and on increased number of cycles, emulsion droplet size was decreased. The size of particles, obtained after adding water at a constant rate, was dependent on the droplet
size in the emulsion. Nanosized particles of 180 nm were obtained using butyl lactate, which concluded the NP formation by the emulsification diffusion process. Because of smaller particle size, the dissolution rate of nano-suspensions increased greatly when compared to commercial product [118].

D. T. Birnbaum et al., determined the influence of the organic phase used during preparation of microparticle on the in vitro release of b-estradiol. Numbers of microparticle formulations were subjected to evaluation for size, shape and in vitro drug release performance. Biodegradable microparticles of PLGA were prepared having b-estradiol which utilized DCM, EA or a mixture of DCM and methanol as the organic solvent for particle preparation. The drug release pattern from the micro sized particles was investigated and comparisons were made of their physical properties for different formulations. The varying solubility’s of b-estradiol and PLGA in the solvents studied resulted in biodegradable microparticles with very different physical characteristics. Microparticles prepared using DCM were similar in appearance to microparticles prepared without drug. Microparticles formulated from DCM/methanol solutions were transparent to translucent in appearance depending on the initial amount of drug used in the preparation. Microparticles formulated using EA showed most uniform encapsulation of drug, appearing as solid white spheres regardless of initial drug content. Constant release pattern was observed with particles formulated using either EA or mixture of DCM and methanol than particles formulated using DCM alone. All formulations showed an initial burst release of drug with increasing drug loading, with indifferent organic solvent used [119].

J Raula et al., prepared nanoparticles of Eudragit L-100 polymer with and without ketoprofen using novel aerosol flow reactor method. Purpose of the study was to study the influence of solvents, solvent mixtures, and co-solute (ketoprofen) on particle morphology. Different solvents used in the study (Ethanol, THF, toluene, and water) were selected according to their vapor pressure and dissolution capability for the polymer. In their study they observed, at the polymer concentration range from 0.2 to 1.5 g/l of the starting solution, the geometric number mean diameters of the particles increased from 75 to 130 nm and from 65 to 100 nm from the solutions of ethanol and THF, respectively. Particles changed from collapsed to irregular via spherical shape in the course of the decreasing solubility of the polymer in the
medium. This critically depends on the solvent evaporation rate as well as the solute solubility. The particle did not change when 10 weight % of ketoprofen was added to the precursor solution [120].

2.5 Stabilizer Profile
2.5.1 Poly Vinyl Alcohol [121]:

Nonproprietary names: PhEur: Poly(vinylis acetas)
USP: Polyvinyl alcohol

Synonyms: Airvol; Alcotex; Elvanol; Gelvatol; Gohsenol; Mowiol; Lemol; Polyvinol; vinyl alcohol polymer; PVA.

Structural Formula

![Structural Formula Image]

Chemical name and CAS registry number: Ethanol, homopolymer [9002-89-5].

Empirical Formula : \((\text{C}_2\text{H}_4\text{O})_n\).

Molecular Weight : 20 000–200 000 g/mol.

Description: It is available as an odourless, white to cream coloured granular powder.

Functional Category: Coating agent; lubricant; stabilizing agent; stabilizing agent; viscosity-increasing agent.

Melting point: 228°C for completely hydrolyzed grades.
180–190°C for moderately hydrolyzed grades.

Refractive index: \(n^25\) D = 1.49–1.53.

Solubility: It is soluble in water, slightly soluble in ethanol (95%) and insoluble in organic solvents. Dissolution requires wetting of PVA in water at room temperature and heating the mixture to about 90°C for roughly 5 minutes. Mixing should be continued while cooling the heated solution to room temperature.

Specific gravity: 1.19–1.31 for solid at 25°C;
1.02 for 10% w/v aqueous solution at 25°C.

Incompatibilities: It reacts with secondary hydroxyl groups and decomposes in strong acids and softens or dissolves in weak acids and alkalis. At higher
concentrations it is incompatible with inorganic salts, especially sulfates and phosphates; precipitation of PVA 5% w/v can be caused by phosphates. PVA solution may undergo gelling in presence of Borax.

**Table 2.1 Commercial grades of polyvinyl alcohol.**

<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>

**Pharmaceutical applications:**

It is used mainly in topical pharmaceutical and opthalmic formulations;
- as a stabilizing agent for emulsions (0.25-3.0% w/v).
- used to increase viscosity of formulations such as ophthalmic products.
- used in artificial tears and contact lens solutions for lubrication purposes, in sustained release formulations for oral administration, and in transdermal patches.
- PVA may be made into microspheres when mixed with a glutaraldehyde solution.

**Table 2.2 Concentration of PVA in dosage forms**

<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>

**Safety:** Generally it is considered as a nontoxic material and up to 10% w/v concentration PVA is non-irritant to the skin and eyes. In cosmetics it is used up to 7% concentrations.

**Handling Precautions:** Normal precautionary measurements have to take as per the circumstances and quantity of material handled. Wearing hand gloves and eye protection are recommended. PVA dust may irritate mucous on inhalation. Handle in a well-ventilated environment.
Stability and Storage Conditions: PVA is stable when preserved in an air tight container in a cool and dry place. PVA solution (aqueous) is stable in corrosion resistant closed containers. Preservatives can be added to the PVA solution if long storage is necessary. PVA undergoes slow degradation at 100°C and rapid degradation at 200 °C; it is stable on exposure to light.

2.5.2 Poloxamer [122]

Nonproprietary Names: BP: Poloxamers
USP-NF: Poloxamer

Synonyms: Lutrol; Pluronic; Monolan; poloxalkol; poloxamera; polyethylene–propylene glycol copolymer; polyoxyethylene–polyoxypropylene copolymer; Supronic; Synperonic.

Chemical Name: α-Hydro-o-droxypoly(oxyethylene)poly(oxypropylene) poly-(oxyethylene) block copolymer.

CAS Registry Number: 9003-11-6.

Empirical Formula and molecular weight: The poloxamer polyols are a series of block copolymers of propylene oxide and ethylene oxide having the chemical formula HO(C₃H₆O)a(C₃H₈O)b(C₂H₄O)a H. The grades included in the PhEur 6.0 and USP32–NF27 is presented in Table 2.3. The PhEur 6.0 states that a suitable antioxidant may be added.

Functional Category: Dispersing agent; emulsifying agent; solubilising agent; tablet lubricant; wetting agent.

Structural Formula

Pharmaceutical applications of poloxamer: These are non-ionic polyoxyethylene–polyoxypropylene copolymers used mainly in pharmaceutical formulations as solubilising agents or emulsifying. The polyoxyethylene and polyoxypropylene segments are hydrophilic and hydrophobic in nature respectively. All types of
poloxamers are chemically similar in composition, differing only in amounts of propylene and ethylene oxides added during manufacture. Different uses of poloxamer are listed in table no 2.4.

**Description:** They are available as white, waxy, free-flowing prilled granules or as cast solids. They are practically odourless and tasteless. At room temperature, poloxamer 124 occurs as a colourless liquid.

**Table 2.3 Grades and molecular weight of poloxamer**

<table>
<thead>
<tr>
<th>Poloxamer</th>
<th>Physical form</th>
<th>A</th>
<th>B</th>
<th>Molecular weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>124</td>
<td>Liquid</td>
<td>12</td>
<td>20</td>
<td>2 090–2 360</td>
</tr>
<tr>
<td>188</td>
<td>Solid</td>
<td>80</td>
<td>27</td>
<td>7 680–9 510</td>
</tr>
<tr>
<td>237</td>
<td>Solid</td>
<td>64</td>
<td>37</td>
<td>6 840–8 830</td>
</tr>
<tr>
<td>338</td>
<td>Solid</td>
<td>141</td>
<td>44</td>
<td>12 700–17 400</td>
</tr>
<tr>
<td>407</td>
<td>Solid</td>
<td>101</td>
<td>56</td>
<td>9 840–14 600</td>
</tr>
</tbody>
</table>

**Typical Properties:**

**Acidity/alkalinity:** pH = 5.0–7.4 for a 2.5% w/v aqueous solution.

**Cloud point** : >100°C for a 1% w/v aqueous solution and a 10% w/v aqueous solution of poloxamer 188.

**Density** : 1.06 g/cm³ at 25°C.

**Flash point** : 260°C

**HLB value** : 0.5–30; 29 for poloxamer 188.

**Melting point**

16°C for poloxamer 124;
52–57°C for poloxamer 188;
49°C for poloxamer 237;
57°C for poloxamer 338;
52–57°C for poloxamer 407.
**Moisture content:** Poloxamers usually contain less than 0.5% (w/w) water and are hygroscopic only at humidity more than 80%.

**Solubility:** Solubility changes as per the type of poloxamer used.

<table>
<thead>
<tr>
<th><strong>Table 2.4 Concentration of poloxamer in different dosage forms</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Use</td>
</tr>
<tr>
<td>Fat emulsifier</td>
</tr>
<tr>
<td>Fluorocarbon emulsifier</td>
</tr>
<tr>
<td>Flavour or solubilizer</td>
</tr>
<tr>
<td>Gelling agent</td>
</tr>
<tr>
<td>Spreading agent</td>
</tr>
<tr>
<td>Stabilizing agent</td>
</tr>
<tr>
<td>Suppository base</td>
</tr>
<tr>
<td>Tablet coating</td>
</tr>
<tr>
<td>Tablet excipients</td>
</tr>
<tr>
<td>Wetting agent</td>
</tr>
</tbody>
</table>

**Surface tension at 25°C:**
- 19.8 dynes/cm for a 0.1% w/v aqueous poloxamer 188 solution;
- 24.0 dynes/cm for a 0.01% w/v aqueous poloxamer 188 solution;
- 26.0 dynes/cm for a 0.001% w/v aqueous poloxamer 188 solution.

**Viscosity (dynamic):** 1000 cP as a melt at 77°C for poloxamer 188.

**Stability and Storage Conditions:** Poloxamers are stable materials. Aqueous solutions of poloxamers are stable with acids, alkalis, and metal ions but support mold growth. It should be preserved in a well-closed container in a cool and dry place.

**Incompatibilities:** It is incompatible with phenols and parabens depending on relative amount.

**Method of Manufacture:** These polymers are manufactured by reacting propylene oxide with propylene glycol to form polyoxypropylene glycol. Ethylene oxide is then added to form the block copolymer.
**Safety:** They are used in different oral, parenteral, and topical pharmaceutical formulations and are generally regarded as nontoxic and non-irritant materials. Poloxamers are not metabolized in the body. Animal toxicity studies, with dogs and rabbits, have shown Poloxamers to be non-irritating and non-sensitizing when applied in 5% w/v and 10% w/v concentration to the eyes, gums, and to the skin. In a 14-day study of IV administration at concentrations up to 0.5 g/kg/day to rabbits, no definite adverse events were noted. A similar study with dogs also showed no adverse event at dosage levels up to 0.5 g/kg/day. In a long-term study, rats fed 3% w/w or 5% w/w of poloxamer in food for up to 2 years did not exhibit any significant symptoms of toxicity. However, albino rats receiving 7.5% w/w of poloxamer in the diet showed some decrease in growth rate. Haemolysis of blood cells (Human) was not observed over 18 hrs at 25°C, with 0.001–10% w/v poloxamer solutions.

**Table 2.5 Solubility of poloxamer in different solvents**

<table>
<thead>
<tr>
<th>Type</th>
<th>Solvent</th>
<th>Ethanol (95%)</th>
<th>Propane-2-ol</th>
<th>Propylene glycol</th>
<th>Water</th>
<th>Xylene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poloxamer 124</td>
<td>Freely soluble</td>
<td>Freely soluble</td>
<td>Freely soluble</td>
<td>Freely soluble</td>
<td>Freely soluble</td>
<td></td>
</tr>
<tr>
<td>Poloxamer 188</td>
<td>Freely soluble</td>
<td>—</td>
<td>—</td>
<td>Freely soluble</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Poloxamer 237</td>
<td>Freely soluble</td>
<td>Freely soluble</td>
<td>—</td>
<td>Freely soluble</td>
<td>SpARINGLY soluble</td>
<td></td>
</tr>
<tr>
<td>Poloxamer 338</td>
<td>Freely soluble</td>
<td>—</td>
<td>SpARINGLY soluble</td>
<td>Freely soluble</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Poloxamer 407</td>
<td>Freely soluble</td>
<td>Freely soluble</td>
<td>—</td>
<td>Freely soluble</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

**Acute animal toxicity data for poloxamer-188:**

LD50 (mouse, IV): 1 g/kg
LD50 (mouse, oral): 15 g/kg
LD50 (mouse, SC): 5.5 g/kg
**Handling Precautions:** Follow normal precautions appropriate to the conditions and quantity of material handled. Wearing of hand gloves and eye protection are recommended.

**Table 2.6 Non-proprietary name and commercial grade of poloxamer**

<table>
<thead>
<tr>
<th>Non-proprietary name</th>
<th>Commercial grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poloxamer 124</td>
<td>L-44</td>
</tr>
<tr>
<td>Poloxamer 188</td>
<td>F-68</td>
</tr>
<tr>
<td>Poloxamer 237</td>
<td>F-87</td>
</tr>
<tr>
<td>Poloxamer 338</td>
<td>F-108</td>
</tr>
<tr>
<td>Poloxamer 407</td>
<td>F-127</td>
</tr>
</tbody>
</table>

Note that in the USA the trade name Pluronic is used.

**2.5.3 Tween 80 [123]:**

It is a polyethylene sorbitol ester having molecular weight of 1,310 Daltons, assuming 1 sorbitol, 20 ethylene oxide units and 1 oleic acid as the primary fatty acid.

**Non-proprietary Names:**
- BP: Polysorbate 80;
- JP: Polysorbate 80;
- PhEur: Polysorbate 80;
- USP-NF: Polysorbate 80.

**Synonyms:** Armotan PMO 2, Atlas E, Cremophor PS 80, Capmul POE-O, Crillet 4, Crillet 50, Drewmulse POE-SMO, Durfax 80, Emrite 6120, E433, Eumulgin SMO, Hodag PSMO-20, Glycosperse O-20, Liposorb O-20K, polysorbatum 80, polyoxyethylene 20 oleate, Protasorb O-20, Ritatate 80, (Z)-sorbitan mono-9-octadecenoate poly(oxy1,2-ethanediyl) derivatives, Tego SMO 80, Tego SMO 80V, polysorbate 80.

**Chemical Name:** Polyoxyethylene (5) sorbitan monooleate.

**CAS No:** 9005-65-6.

**Empirical Formula:** $C_{64}H_{124}O_{26}$.

**Molecular weight:** 1310 g/mol.
**Functional Category:** Dispersing agent, emulsifying agent, non-ionic surfactant, solubilising agent, suspending agent and wetting agent.

**Structural Formula**

![Structural Formula Image]

**Pharmaceutical applications:** Polysorbates having 20 oxyethylene units are hydrophilic and non-ionic surfactants, which are used widely as emulsifier in the preparation of stable o/w pharmaceutical emulsions. They can also use as solubilising agents for different substances including essential oils and oil-soluble vitamins and as wetting agents in the formulation of oral and parenteral suspensions. They also found increasing the oral bioavailability of drugs that are substrates for P-glycoprotein.

**Description:** Polysorbates have a characteristic odour and a warm, somewhat bitter taste and available as Yellow oily liquid at 25°C.

**Table 2.7 Concentration of tween-80 in different dosage forms.**

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (in % w/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emulsifying agent</td>
<td></td>
</tr>
<tr>
<td>alone in o/w emulsions</td>
<td>1–15</td>
</tr>
<tr>
<td>In combination with hydrophilic emulsifiers in o/w 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>Used as solubilizing agent for poorly soluble active constituents in lipophilic Bases</td>
<td>1–15</td>
</tr>
<tr>
<td>Wetting agent</td>
<td></td>
</tr>
<tr>
<td>For insoluble active constituents in lipophilic bases</td>
<td>0.1–3</td>
</tr>
</tbody>
</table>
Typical Properties:

**Acid value see (%)** : 2.0.

**pH** : 6.0–8.0 for a 5% w/v aqueous solution.

**Flash point** : 149°C.

**HLB value** : 15.0.

**Hydroxyl value** : 65-80.

**Saponification value** : 45-55.

**Solubility** : Soluble in ethanol and water. Insoluble in vegetable and mineral oils

**Specific gravity (25°C)**: 1.08.

**Surface tension for 0.1% w/v solutions (25°C)**: 42.5 (mN/m).

**Viscosity (dynamic)**: 425 mPas.

Stability and Storage Conditions: Polysorbates esters are stable to electrolytes and weak acids and bases; gradual saponification occurs with strong acids and bases. The oleic acid esters are prone to oxidation. They are hygroscopic and should be analyzed for water content before use and dried if needed. Also, in common with other polyoxyethylene surfactants, prolonged storage can lead to the formation of peroxides. They should be stored in air tight container, protected from light, in a cool and dry place.

Incompatibilities: Discoloration and precipitation may occur with variety of substances, especially phenols, tars, tar like material and tannins. The antimicrobial activity of parabens is reduced in the presence of polysorbates.

Method of Manufacture: Polysorbates are prepared from sorbitol in a three-step process. Initially water is removed from sorbitol to get sorbitan (a cyclic sorbitol anhydride). The sorbitan is then partially esterified with a fatty acid, such as oleic or stearic acid, to yield a hexitan ester. Finally, ethylene oxide is chemically added in the presence of a catalyst to yield the polysorbate.

Safety: They are widely used in oral, parenteral and topical pharmaceutical formulations, cosmetics, food products and are skin irritant.

Handling Precautions: Follow normal precautionary steps appropriate to the conditions and amount of material handled. Eye protection and gloves are recommended.
**Regulatory Status:** Polysorbate-80 is GRAS listed and also as food additives in Europe. Polysorbate-80 is included in the FDA Inactive Ingredients Database (IM, IV, oral, rectal, topical, and vaginal preparations).