1. INTRODUCTION AND REVIEW OF LITERATURE

The stratum corneum is a barrier, which prevents drug penetration into the skin. The property of skin permeation of a drug moiety from topical formulation is affected by some of the factors, e.g. release of the drug molecules from the dosage form (diffusion through adhesive layer), sorption of the drug(s) onto the surface layer of the stratum corneum (portioning of the drug from the adhesive layer to the stratum corneum of the skin), diffusion through stratum corneum, entry into a layer of the dermis, and spreading (1).

There are some necessities of drug candidates used for topical and/or ophthalmic drug delivery system as reported in Table 1.1 (2, 3).

Table 1.1: Ideal properties of a drug candidate

<table>
<thead>
<tr>
<th>Properties</th>
<th>Necessary criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>Should be low (less than 10 mg)</td>
</tr>
<tr>
<td>Half-life</td>
<td>10 h or less</td>
</tr>
<tr>
<td>Molecular weight*</td>
<td>800 Dalton or less; desirably 500 Dalton or less, the limit could indeed more than 500 Daltons, but still efficiently permeate the skin via passive diffusion (4)</td>
</tr>
<tr>
<td>Partition coefficient</td>
<td>Log p (octanol-water) between 0.8 and 5</td>
</tr>
<tr>
<td>Skin permeability coefficient</td>
<td>More than $0.5 \times 10^{-3}$ cm/h.</td>
</tr>
<tr>
<td>Skin reaction</td>
<td>Non-irritating and non-sensitizer</td>
</tr>
<tr>
<td>Oral bioavailability</td>
<td>Low</td>
</tr>
<tr>
<td>Therapeutic index</td>
<td>Low</td>
</tr>
<tr>
<td>Polarity</td>
<td>Less</td>
</tr>
<tr>
<td>Molecular Size</td>
<td>Small</td>
</tr>
<tr>
<td>pKa</td>
<td>High</td>
</tr>
<tr>
<td>Melting point</td>
<td>Low</td>
</tr>
</tbody>
</table>

*For non-diseased skin; pKa: Acid dissociation constant at logarithmic scale

Lipophilicity is non-linear and is the relationship between log p-value and permeation. The permeation is decreasing at both low and high end of log p-values. Therefore, log p-value of 5 is often considered as the upper limit of desired lipophilicity. The oil-water partition coefficient of a substance gives an idea about its lipophilicity and hydrophobicity (5). Same way the excipients utilized for topical or ophthalmic drug delivery system should also have some requirement for topical formulations as reported in Table 1.2 (6, 7).
Table 1.2: Ideal properties of excipient candidate

<table>
<thead>
<tr>
<th>Properties</th>
<th>Necessary criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin reaction</td>
<td>No-irritant and no allergic</td>
</tr>
<tr>
<td>Effects on final preparation</td>
<td>Little/ no deleterious</td>
</tr>
<tr>
<td>Regulatory status</td>
<td>IIG listed, GRAS listed or biologically safe</td>
</tr>
<tr>
<td>Concentration</td>
<td>Under regulatory limit</td>
</tr>
<tr>
<td>Compatibility</td>
<td>Compatible with API and the other excipients</td>
</tr>
</tbody>
</table>

IIG: Inactive ingredient guideline, GRAS: Generally, referred to as safe, API: Active pharmaceutical ingredients.

Most of the antimicrobial agents are hydrophobic in nature. Therefore, they have the problems of solubility, permeability, partition, diffusion, dissociation, and penetration. Among available antimicrobial therapies like topical, oral and intravenous preparations, the intravenous preparations have good action but have serious unwanted side effects. Cream and gel have bigger globule size and ointment has less patient compliance. Therefore, topical preparations (e.g. cream, gel, ointment, etc.) have disadvantages of less penetration.

To solubilize 10 % w/w Salicylic in water is difficult because solubility of salicylic acid is 2.24 mg/g in water (0.224 % w/w) (8). Intravenous and oral preparations cannot prepare for 10 % w/w Salicylic acid (9) and for keratolytic action. The available formulation of 10 % w/w Salicylic acid in Methanol have skin cracking problem on rapid applications because solubility of salicylic acid is 625 mg/g (62.5 % w/w) in Methanol (10). Patients have preferred only topical preparations in fungal infections. The available semisolid formulations have disadvantages of being greasy in nature of base and free crystals of Salicylic acid available for action leads in skin irritation (11). In respect to adverse effects of high concentration of Salicylic acid, the formulations of Salicylic acid for topical application is required to be justified.

Oral preparations lead to degradation by gastrointestinal fluid and the first pass mechanisms. Therefore, Ciprofloxacin has lesser oral bioavailability. Also, rapid applications of oral ciprofloxacin have side effects like intestinal perforation, gastrointestinal tract bleeding, jaundice, and pancreatitis. Patients are preferred only topical preparations in acne. Available topical formulations for acne cause irritant contact dermatitis (12) and Ciprofloxacin is well-
established for bacterial conjunctivitis (13). Gel and cream have bigger globule size available for drug action and ointment has less patient compliance because of greasy nature. Ciprofloxacin has poor skin retention and low permeability across stratum corneum (14). Therefore, there is a need of topical Ciprofloxacin formulation which has sustain action and high skin penetration without systematic adverse effects.

Oral and intravenous formulations cannot prepare for Chloramphenicol because Chloramphenicol has resistance to human in different parts of India (15). Ocular infection isolates have not developed resistance to Chloramphenicol, so it is recommended in ocular infections (16). Patients are not fully satisfied with over-the-counter allergic conjunctivitis relief ophthalmic formulations (17). Patients have preferred ophthalmic preparations in red eye disease(s) (seasonal allergic conjunctivitis, perennial allergic conjunctivitis, atopic keratoconjunctivitis, and vernal keratoconjunctivitis). Ointment (Chloramphenicol eye cap) has less patient compliance because of it has poor vision problem after application due to greasy nature. Conventional ophthalmic formulations (solution and suspension) have the pre-corneal elimination of Chloramphenicol which result into poor bioavailability in the ocular cavity (18) because it has high water solubility (2.5 mg/g; 0.25 % w/w) (19). Therefore, need of new formulation which retain Chloramphenicol at the conjunctiva without drain into throat.

Emulsions are two-phase systems of two or more non-miscible liquids. Generally, the oil(s) is dispersed into the water and vice versa. There are several types of emulsions as oil-in-water (o/w), water-in-oil (w/o), oil-in-oil (o/o), microemulsions, double emulsion, multiple emulsion, and mixed emulsions. For preparation and stability of the emulsion, the emulsifier is necessary. Various factors have affected the process of emulsification, such as the nature of oil, emulsifier(s), the concentration of emulsifier(s), temperature, and methods of preparation (1).

Emulgel is prepared by a combination of emulsion and gel. It has been recently used as a vehicle to deliver various drug(s) to the skin for local and systemic action(s). In fact, the presence of the gelling agent in the water
phase converts an ancient emulsion into emulgel (20). The direct (o/w) emulsion is used to entrap lipophilic drugs, while emulgels encapsulated hydrophilic drugs in reverse (w/o) system (21, 22). Emulgels have a certain degree of elegance and are easily washable whenever required. As an unionized form of the drug is absorbed rapidly through the cell membrane (5), it has a high ability to penetrate across the skin. Topically used emulgels have several desirable properties like being thixotropic, greaseless, easily spreadable, removable, emollient, non-staining, water-soluble, longer shelf-life, bio-friendly, transparent, and pleasant appearance (23-25).

1.1 Review of Literature

1.1.1 Review of Literature Regarding Emulsion

Madaan et al., (2014) stated that emulsions are thermodynamically unstable heterogeneous biphasic system. Physical and chemical instability of emulsion is checked by cream formation, cracking, phase inversion, flocculation, rheological properties, macroscopic examination, globule size analysis, and accelerated stability study. The film forming emulgents are formed a monomolecular, multimolecular, and particulate film around dispersed phase globules. Several technologies made enhancements for improvement in the effectiveness and stability of the emulsion. Technologies available for preparation of emulsions are a microemulsion, multiple emulsion, non-aqueous emulsion, liposome emulsion, nanoemulsion, and emulsion polymerization (26).

Khan et al., (2014) compared the effectiveness of emulsion formulations containing plant extracts (Hippophae rhamnoides and Cassia fistula) with placebo emulsion. A significant decrease in the level of sebum contents is observed in the patients who have used emulsions containing the plant extract. The difference between pre- and post-treatment levels of sebum contents is statistically significant (p ≤ 0.05). Emulsions containing plant extracts are useful in the reduction of skin sebum contents (anti-acne effects) as compared to placebo (p ≤ 0.05). The topical emulsion has good penetration property (27).
Tadros et al., (2015) revealed that emulsions are a class of disperse systems consisting of two immiscible liquids and is the dispersion of the disperse phase in the continuous phase. A third component (emulsifier) is needed to mix two immiscible liquids. The choice of the emulsifier is crucial in the formation of the emulsion and its stability. The solubility of the dispersed droplets and the globule size distribution is determined by Ostwald ripening. Stability of the liquid film between the droplets determines coalescence (1).

Practical Sciences Drug development service (2011) stated that emulsions encompass a vast number of everyday materials and products. Topical emulsions of both o/w and w/o types are commonly used to improve aesthetics and ease of application. Emulsions may be used to deliver multiple drugs by improving solubilities, the distribution, and permeation. However, as emulsions are inherently thermodynamically unstable, understanding of the theoretical factors influencing emulsion stability is critical to the emulsion formulator (28).

Neeraja et al., (2014) used emulsions to enhance the bioavailability of various drugs as a prolonged drug delivery system. In this study, a two-step emulsification method using Tween and Span 40 is preferred for the preparation of multiple emulsion of Nifedipine. Emulsion evaluated for stability, percentage Nifedipine entrapment, and in vitro Nifedipine release. Fourier Transform Infra-Red (FTIR) studies indicated that there is no chemical interaction in the mixtures. Dissolution studies have shown that in vitro release profile of the Nifedipine improved by Span 40. The study concluded that the multiple emulsions are useful for the improvement of dissolution rate and oral bioavailability of poorly water-soluble drug (Nifedipine) (29).

Christine et al., (2013) performed an open-label medication study that reported the efficacy of an emulsion (artificial tear) for the treatment of dry eye associated with meibomian gland dysfunction. At baseline, 49 patients had low and mild to moderate meibomian. Eye drops are administered 2.5 ± 1.3 times/day. After 4 weeks of medication, the emulsion has significant clinical recovery (p ≤ 0.05). Visual acuity is remained statistically similar, while corneal staining and tear film breakup time improved significantly (p ≤ 0.05). However, modestly, the outcomes are achieved with 1.9 ± 1.1 doses/day of study medication, a significantly lower frequency than the habitual frequency
The most common medication-related adverse event is blurred vision (3/49 patients, 6.1 %) and habituation 27/44 (61.4 %). The study concluded that the artificial tear emulsion is effective for treating the signs and symptoms of dry eye (30).

Noda et al., (2013) noticed that maintenance of proper moisture and regulation of infection are simultaneously required to promote healing of pressure ulcers. Continuous use of water-rich ointment may often lead to excess moisture and induce edematous granulation tissue. Use of watersoluble ointment may excessively absorb, exudate, and induce dry granulation tissue. Selection of appropriate topical ointment is desired to avoid worse clinical outcomes. For adjustment of wound moisture, a novel blended ointment (tretinoin tocopheryl-povidone-iodine (TR-PI)) is developed consisting of emulsion base, tretinoin tocopheryl o/w emulsion (TR-cream), sugar base, povidone-iodine, and sugar (PI-sugar). Water absorption rate constant of TR-PI with combination ratio of PI-sugar at 75 % (TR-PI75, 18.5 mg cm\(^{-2}\) min\(^{-0.5}\)) was equivalent to that of TR-cream alone (16.4 mg cm\(^{-2}\) min\(^{-0.5}\)). The yield value of TR-PI75 (26.1 Pa) is exhibited intermediate values as compared to those of TR-PI with combination ratio of PI-sugar at 50 % (11.3 Pa) and TR-cream alone (46.8 Pa). The amount of released free-iodine from TR-PI75 is similar to that released from PI-sugar alone. TR-PI75 may have superior performance in keeping the moist environment in wounds and in preventing infection. TR-PI75 can be used to promote the formation of favorable granulation tissue in pressure ulcers with moderate exudates (31).

Stonecipher et al., (2013) designed to assess patterns of topical 0.05 % w/w Cyclosporine ophthalmic emulsion in dry eye patients. The primary endpoint is a percentage of patients with at least one primary vs. no primary dry eye diagnosis who have filled a topical Cyclosporine prescription. Data analyzed included utilization of topical corticosteroids, oral tetracyclines, and punctual plugs. The analysis included 576,416 patients, accounting for 875,692 dry eye outpatient visits. Seventy-five percentages are female, 64 % are age’s 40–69 years, and 84 % have at least one primary dry eye diagnosis. 16 % of dry eye patients with a primary diagnosis vs. 6.5 % with no primary diagnosis are filled at least one Cyclosporine prescription. For patients who have filled at least one prescription, the mean months’ supply of Cyclosporine filled over 12-
months is 4.44. Overall, 34 % of dry eye patients filled a prescription for topical Cyclosporine, topical Corticosteroid, or oral Tetracycline over two years. Patients with a primary dry eye diagnosis are more likely to fill a topical Cyclosporine prescription. Although inflammation is key to the pathophysiology of dry eye, most patients seeing a physician for dry eye may not receive anti-inflammatory therapies (32).

Zyl et al., (2015) investigated the effect of evening Primrose oil, Vitamin F, and Pheroid™ technology on the transdermal delivery of cream-based Flurbiprofen formulation. The research is performed for membrane release studies. The results are indicated the order for Flurbiprofen release as Vitamin F >> control (no penetration enhancers) > evening Primrose oil >> Pheroid™. Topical skin delivery results indicated that Flurbiprofen is present in the stratum corneum, epidermis, and the dermis. Average percentage Flurbiprofen diffused to the receptor phase (representing human blood) indicated that evening Primrose oil formulation showed the highest average percentage diffused. Pheroid™ formulation delivered the lowest concentration with a statistically significant difference ($p \leq 0.05$) compared with the control formulation (containing 1 % Flurbiprofen). The control formulation presented the highest average flux with evening Primrose oil formulation. The study concluded that evening Primrose oil is the most favorable chemical penetration enhancer when used in emulsion (33).

Waqas et al., (2016) developed a w/o emulsion containing grape seed extract for application in cosmeceuticals. The dried grape seeds have extracted with the hydroalcoholic mixture and developed emulsions consisting of different concentrations of Cetyltrimethicone (ABIL EM90), the nonionic emulsifier, liquid paraffin (oil phase), and water. The formulated emulsions are observed for pH, viscosity, liquefaction, and thermal stability. The stable formulation consists of 16 % of Mineral oil, 4 % of ABIL EM 90®, 4 % of Grape seeds extract, 1 % of Rose oil, and 75 % of water. All the results derived from the study showed excellent stability over 3-months period, which indicated that w/o emulsion could use as a carrier of 4 % of grape seeds extract to enhance desired effects (34).

Gade et al., (2015) formulated a stable w/o emulsion containing Fenugreek seeds extract using Olive oil. The emulsion entrapped the extract of
Fenugreek seeds in the inner aqueous phase (w/o emulsion). The herbal formulations have shown good spreadability, consistency, and homogeneity, desirable pH, and non-greasiness. Emulsions are stable in respect to color, liquefaction, and phase separation at all the accelerated conditions. The extract-containing cream has substantially increased skin elasticity, hydration, and decreased the skin melanin (35).

**Sane et al., (2013)** developed a formulation of Elacridar to overcome its dissolution-rate limited bioavailability. Physicians restricted Elacridar, for the chronic use due to poor solubility and poor oral bioavailability. Elacridar emulsion is found to be effective. Mice are used to determine the bioavailability of Elacridar after a 10 mg/kg dose in the emulsion, intraperitoneally and orally. The absolute bioavailability is determined to be 1.3 and 0.47, respectively. The coadministration of Elacridar emulsion intraperitoneally with oral Erlotinib in mice improved 3-fold Erlotinib brain penetration. The current study shows that an emulsion formulation of Elacridar is effective in improving the bioavailability. Emulsion offers an alternative to the suspension and allows a decrease in the dose required to achieve a significant effect (36).

**Kedar et al., (2012)** developed o/w type emulsion from Karanj, Castor, and Neem oils. Various physicochemical parameters and stability study are evaluated. The rheological characterization has shown that emulsions have a sprayable product (Pseudoplastic flow nature) and promising activity (37).

**Buyukozturk et al., (2010)** investigated the influences of design on physicochemical properties and associated function in the gastrointestinal environment of self-emulsifying drug delivery systems. Two critical functions of emulsion-based drug delivery systems, permeability enhancement, and drug release are studied. Oil, emulsifiers (hydrophilic-lipophilic balance (HLB)) concentrations and the emulsifier-to-oil ratios are evaluated. The study is combined for three emulsifiers with HLB values from 10–15 at three different oil: emulsifier ratios (1:1, 5:1, 9:1) and has calculated release coefficients for each emulsion system. Unstable formulations of low HLB emulsifier (HLB = 10) has a toxic effect on cells at high (1:1) emulsifier concentrations, indicating the importance of formulation stability for minimizing toxicity. Results also indicated that high HLB emulsifier (Tween 80) has loosened tight
junction at high surfactant concentrations (1:1). Incorporation of a long chain triglyceride (Soybean oil) as the oil phase is increased the drug release rate. These results are established as an initial foundation for relating emulsion function to formulate a design, enabling bioavailability, and optimization across a broad representative range of self-emulsifying drug delivery systems (38).

1.1.2 Review of Literature Regarding Emulgel

Joshi et al., (2012) worked on the topical delivery of Clarithromycin emulsion based gel. Emulgel prepared using HPMC K4M (Hydroxypropyl methylcellulose, high molecular weight) and Carbomer 940/934. Emulgel has dual control release system i.e. gel and emulsion, offers potential advantages of delivering Clarithromycin directly to the site of action and extended period of time, has possessed very high viscosity, transparency, film-forming properties at low concentration, and reported to be useful formulation with an objective to increase transparency and spreadability. Prepared emulgels have shown acceptable physical properties and in vitro Clarithromycin release profile (39).

Caillett et al., (2012) invented topical pharmaceutical composition comprising the Diclofenac diethylammonium salt in unusually high amounts. The prepared compositions represent opaque emulsion-gels with unique properties such as high skin penetration, no irritation, high stability, complete dissolution of Diclofenac diethylammonium, and high pain relief (40).

Jain et al., (2010) investigated the emulgel for enhancement of topical delivery of Ketoconazole using Carbomer 934 and 940. Influence of type and concentration of the gelling agent, an oil phase, and emulsifying agent on Ketoconazole release from prepared emulgel is investigated using a $2^3$-factorial design. The antifungal activities and Ketoconazole release have found to be higher for an optimized batch of emulgel as compared to the marketed Ketoconazole cream. The emulgels have sustained Ketoconazole delivery in a controlled manner with a comparison to marketed formulation (41).
Patel et al., (2012) developed jellified emulsion of hydrophobic Glucosamine sulfate for transdermal drug delivery using Carbomer 934 and HPMC K-100 in gel: emulsion ratios of 1:1 and 1:1.5. The emulgel evaluated for their various parameters. The optimized formulation showed high solubility of the hydrophobic Glucosamine, increased permeability across the skin, and modified release (42).

Khullar et al., (2012) prepared emulgel of Mefenamic acid using Carbomer 940, Mentha oil, and Clove oil (penetration enhancers). The prepared emulsion incorporated in a gel base. The formulations have shown comparable analgesic and anti-inflammatory activity with marketed Diclofenac sodium gel. The results concluded that topical emulgel of Mefenamic acid has possessed an effective anti-inflammatory and analgesic activity. The emulgel has good Mefenamic acid delivery across the skin (25).

Singla et al., (2012) prepared emulgel of Lornoxicam from Carbopol 934, 940, and HPMC-K4M using Mentha oil as a permeation enhancer. Prepared emulgel has better Lornoxicam penetration and acceptable physicochemical properties (43).

Ajazuddin et al., (2013) reported that emulgels are o/w or w/o type emulsion-based gel. In emulgel, the emulsion is gelified by mixing with a gelling agent. Incorporation of emulsion into gel increases its stability and makes it-a dual control release system. Due to lack of excess oily bases and insoluble excipients, it shows better drug release as compared to the other topical drug delivery system. The presence of gel phase makes it a non-greasy and has better patient compliance (44).

Ghodekar et al., (2012) carried out a study to increase the solubility and bioavailability of Silver sulphadiazine by formulating emulgel. Poloxamer 407, Poloxamer 188, and solid dispersions of Poloxamer 407 are more amorphous than solid dispersions of Poloxamer 188. Sepineo™ P 600 lecithin emulgel has high Silver sulphadiazine release and better gel characteristics compared to Pluronic lecithin and Carbomer-Lecithin gel (45).

Marwaha et al., (2013) prepared topical emulgels of a powdered extract of Commiphora Mukul and Babchi oil. In vitro studies indicated that marketed Tacrolimus ointment and optimized formulation have released 79.72 % and 94.34 % of Tacrolimus in 6 h. Moreover, the emulgel containing Commiphora
Mukul and Babchi oil have overcome the side effects posed by Tacrolimus (46).

Singpho et al., (2014) developed and evaluated semisolid formulations of agar-gelatin hydrogels, emulgels, and bigels of Metronidazole. Hydrogels have used agar and gelatin for the preparation. Emulgels have used Soybeans oil for the preparation. Organogel is prepared using Soybeans oil as a solvent and Stearic acid as oregano gelator. The bigel is prepared by mixing organogels with the agar-gelatin hydrogel. The prepared gels are characterized by their surface morphology, mechanical properties, chemical interactions, electrical properties, and the surface Topography. XRD study established the amorphous nature of the gels. FTIR study has confirmed the interpolymeric bonding between gelatin and agar as well as encapsulation of Soybeans oil within the polymeric matrix and no interaction between the polymers and Metronidazole. The hydrogels have shown lower impedance than emulgels and bigels indicating the higher content of aqueous phase within it. The hemocompatibility test confirmed the blood compatibility of the preparations. The emulgel has shown least mucoadhesive characteristic, while the hydrogel sample have shown the highest mucoadhesion. The leaching study has confirmed the presence of oils in the samples. The swelling profiles for the formulations are in tune with in vitro release studies in pH 7.2 phosphate buffer. The antimicrobial effect of all the Metronidazole-loaded emulgel is found to be superior (47).

Khalil et al., (2011) formulated topically applied emulgel of Clotrimazole from different formulas. All the prepared emulgels have shown acceptable physical properties. The rheological studies have revealed that all emulgels exhibited a shear thinning behavior. Clotrimazole emulgels have exhibited higher Clotrimazole release than Canestin® cream. The emulsifying agent concentration has the most pronounced effect on the Clotrimazole release from the emulgels, followed by the oil phase concentration, which has a retardation effect and finally the type of the gelling agent (48).

Digennaro et al., (2015) evaluated the safety and effectiveness of a new medical treatment based emulgel with emollient, soothing, and protective agents in patients with anal fissuring. The study proved that emulgel has as an effective and well-tolerated topical treatment for both acute and chronic anal
fissuring in the short term. The finding is constituting one more arrow to the bow of proctologists in treating painful disease and compared well with the other conservative medical treatments even if the long-term outcome (49).

Chunmei et al., (2011) investigated the influence of different grades of Carbomer and penetration enhancers on the percutaneous permeation of Tetrahydropalmatine. The rheological analyses have done for steady flow tests, oscillation stress sweep, and creep recovery. The emulgel prepared with Carbopol® 971P has the matrix and N-methyl-2-pyrrolidone (penetration enhancer) has the highest cumulative permeation amount. All the experimental data have shown an excellent fit to the Casson model irrespective of penetration enhancers used. The release profile of emulgel with Carbopol® 971P as the matrix without any penetration enhancers is fitted to zero-order release kinetics model. However, on the addition of penetration enhancers, in vitro release of Tetrahydropalmatine is presented anomalous (non-Fickian) release kinetics (50).

Varma et al., (2014) formulated and evaluated an emulgel containing Calcipotriol for the treatment of psoriasis. Isopropyl alcohol and Polyethylene glycol have employed as permeation enhancers. Carbomer is reported to have a direct influence on appearance and viscosity of the final formulation. The photo-microscopic evaluations have shown the presence of spherical globules in size range of 10–15 µm. The rheogram revealed that all the formulations exhibited pseudoplastic flow. The optimized formulation has 86.42 ± 2.0 % Calcipotriol released at the end of 8 h. The release rate across dialysis membrane and rat skin is higher when compared to commercial Calcipotriol ointment. It is concluded that emulgels are a promising delivery system for the delivery of Calcipotriol (hydrophobic drugs). (51).

Basera et al., (2015) reported that use of emulgels could be considered for analgesics and antifungal drugs. It has been great interest in the use of a novel polymer with a complex function (emulsifiers and thickeners). The gelling capacity of the compounds stabilized the emulsion and creams by decreasing surface and interfacial tension and increasing the viscosity of aqueous phase. Despite many advantages of gels, a major limitation is delivery of the hydrophobic drug. To overcome this limitation an emulsion-based gel approach is used (52).
Introduction and Review of Literature

Sabu *et al.*, (2013) formulated an emulgel of Terbinafine HCl using Carbomer 934. Emulgel has improved the stability of the emulsion, reduced dosage regimen, and enhanced residence time in the treatment of fungal infection. The effect of concentration of the oil phase and emulsifying agent on the release of Terbinafine HCl is investigated using a $2^2$-factorial design. The physicochemical properties of developed emulgels are evaluated. Terbinafine HCl release is found to be higher for optimized formulation as compared to the marketed formulation (Terbinafine HCl cream). Terbinafine HCl releases from all the emulgels are followed diffusion-controlled mechanism. Stability study indicated that the physical appearance, rheological properties, spreadability, and Terbinafine HCl release in all the prepared emulgels are remained unchanged upon storage (53).

Teku *et al.*, (2015) worked on natural gums (Badam gum and gum Karaya) in the preparation of emulgel using Capsaicin (as an analgesic). Emulgel has used Peppermint oil (oil phase), the combination of Span 20 and Tween 80 (emulsifying agent), and Eucalyptus oil (permeation enhancer) in different concentrations. The phase inversion technique is used for the preparation of o/w emulsion. Prepared emulsion is evaluated for the type of emulsion formed, Capsaicin content, and globule size. The emulgel containing 9% of Badam gum and 12% of gum Karaya is selected as an optimized batch based on consistency, physicochemical properties, skin irritation, *in vitro*, and *ex vivo* Capsaicin release. The optimized batch is compared with the marketed formulation pain relieving gel patch (Capsaicin 0.025%) for *in vitro* Capsaicin release. The results obtained from flux data revealed that optimized formulation is superior to the marketed formulation (54).

D'Souza *et al.*, (2015) prepared emulgels using suitable permeation enhancer(s) to enhance the permeation of the Meloxicam through the skin. Emulgels have used Tween 20 and Span 20 as emulsifiers, HPMC K4 and Carbomer 934 as gelling agents, Menthol, Clove oil, Isopropyl myristate, Dimethyl sulfoxide (DMSO), and Oleic acid as permeation enhancers. The prepared emulgels are evaluated for their physicochemical properties and *in vitro* Meloxicam release. The release profile of Meloxicam exhibited zero-order kinetics and obtained data have fitted well with Higuchi's equation.
following non-Fickian mechanism. Emulgel containing Meloxicam is a promising delivery system for the treatment of rheumatoid arthritis (55).

Ambala et al., (2015) formulated Ketoprofen emulgels using different viscosity grades of HPMC and Carbomer as gelling agents. All the prepared emulgels have shown acceptable physical properties. The study has investigated the influence of the type of gelling agent on the release of Ketoprofen from the emulgels. Carbomer 934 has shown good results not only in the release of Ketoprofen but also in physical parameters. Formulations with Carbomer in low concentration compared to HPMC K4M and K15M in high concentrations has better-controlled release. FTIR study has proved the compatibility between Ketoprofen and the other excipients. From the stability studies, similarity index value between dissolution profiles of the optimized formulation before and after storage is found to be within the limit. The development of Ketoprofen emulgels is a suitable way for topical administration (56).

Patel et al., (2015) formulated Isotretinoin microemulsion based gel using Isopropyl myristate, Labrasol, Plurol oleique, and water. The microemulsion-based gel has shown desired physicochemical parameters and demonstrated advantages over marketed formulation in improving the skin tolerability of Isotretinoin, indicating its potential in improving topical delivery. The study concluded that the developed microemulsion based gel has good potential for the treatment of acne (57).

Kusuma et al., (2015) developed and optimized the emulgel system for Indomethacin using Carbopol 934, HPMC K4M, Xanthan gum, and pregelatinized Ipomoea batata starch (as gelling agents). The prepared emulgels are evaluated for physical and chemical characteristics, in vitro Indomethacin release, and accelerated stability studies. The results found that Indomethacin release followed zero order kinetics and to be stable in varying temperature and acceptable physical properties. The Indomethacin emulgel formulation prepared with pregelatinized Ipomoea batata starch having the oil phase concentration in its low level and emulsifying agent concentration in its high level is the formula of choice (58).

Al-saraf et al., (2016) reported that Itraconazole has side effects such as nausea, vomiting, hypokalemia, and skin rash when taken orally.
Physicochemical parameters, *in vitro* release, and skin irritation studies of the prepared Itraconazole emulgels are evaluated. The results showed a wider zone of inhibition for the Itraconazole emulgel as compared with marketed cream. The emulgel has no edema, no erythema, and demonstrated the shear thinning thixotropic behavior. Hence it concluded that emulgel is more effective and safe for delivery of Itraconazole (Biopharmaceutics classification system (BCS) class II drug) (59).

**Singh et al., (2014)** worked on Clindamycin phosphate emulgel using HPMC-5 and HPMC-15 (high molecular weighted and water-soluble), Carbopol 934, and Carbopol 940 with Oleic acid (as a permeation enhancer). The study reported that emulgels are possessed very high viscosity, transparency, and film-forming properties at low concentration. The prepared emulgels have shown acceptable physical and chemical properties, *in vitro* diffusion, *ex vivo* release, and stability (60).

**Bonacucina et al., (2009)** revealed that Sepineo™ P 600 (concentrated dispersion of acrylamide/sodium acryloyldimethyltaurate copolymer in isohexadecane) has self-gelling and thickening properties. Gel-in-oil formulations have been prepared using a Sepineo™ P 600 in the concentration range of 0.5–5 % w/w. All the prepared gel-in-oil are analyzed for oscillation rheology, acoustic spectroscopy, the particle size of the oil droplets, and the microrheological extensional moduli (G’ and G”). Both rheology and acoustic spectroscopy indicated that addition of the oily phase is caused minimal changes to the elastic character of the gel. Sepineo™ P 600 gel-in-oil is active systems for use in local and other types of applications (61).

**Dong et al., (2015)** investigated the relationships between rheological characters, *in vitro* diffusion, and percutaneous permeation profiles of Terpinen-4-ol across Cellophane membrane and excised rabbit skin conducted by Franz diffusion cell. All of the emulgel samples have shown a non-uniform bimodal distribution and the microstructure represented a matrix type, which inhibits the diffusion of oil globules in the formulation to some extent. Rheological data have shown an excellent fit to the Herschel–Bulkley model in Viscosimetric studies regardless of the polymers used. Moreover, 10 % of Sepiplus 400 has obtained the highest zero-shear viscosity, G’, G” values and lowest Τ₉₅% G value corresponding to the strongest structure. The
results of in vitro release tests have revealed that an increase in viscosity might affect the release profiles inversely, irrespective of the polymers used. In vitro permeation of Terpinen-4-ol indicated that when the Terpinen-4-ol amount released could satisfy the essential driving force. Permeation processes are independent of release (62).

Shah et al., (2016) reported that emulgel is a unique topical delivery system for ophthalmic, vaginal, skin, and rectal routes for a healthy as well as diseased skin. Gel has a limitation in the delivery of hydrophobic drug moiety. Emulgel has properties of both gel and emulsion and shows dual release control system. Emulgel has facilitated the delivery of the hydrophobic drug via skin with control delivery (63).

Berdey et al., (2016) evaluated viscoelastic properties and rheological characterization of emulgel with natural, synthetic, and semisynthetic gelling agents. Among semisolid drugs formulation, an emulgel is one of the most preferred formulations. Emulgels are emulsions that are gelled by mixing with a gelling agent. They possessed advantages of emulsions and gels, ease of spreadability, the convenience of viscosity, appearance, and emollient effect. The gelling agent has an appreciable influence on rheological properties of emulgels. The prepared emulgels have exhibited non-Newtonian shear thinning behavior with thixotropy. Emulgels showed excellent stability and the consistent rheological model under different treatment conditions (64).

Yapar et al., (2013) developed a stable and easily manufactured emulgel including green tea extract and Rose oil that is effective on the barrier function and hydration of the skin. An emulgel formulation containing 20 % green tea extract and 5 % Rose oil is designed as a result of pre-formulation studies. Physicochemical characterization, in vivo water content of the stratum corneum, trans-epidermal water loss, and in vitro stability studies revealed that a cosmetically acceptable, stable, and productive emulgel formulation for skin barrier function with excellent hydrating properties is obtained for skin hydration, protection, and anti-aging purposes (65).

Andonova et al., (2014) evaluated an in vitro release of Ketoprofen from the prepared emulgels. The different quantity of light liquid paraffin (5–7.5 %) and Carbomer 940 are used for the preparation of emulgels. The resulting emulgels are homogeneous with suitable consistency, have excellent
appearance, and acceptable pH for skin application. If the oil phase is increased the amount of release of Ketoprofen is also increased (66).

1.1.3 Review of Literature Regarding Salicylic Acid

Badawi et al., (2009) reported that Salicylic acid has a keratolytic effect when used in topical products. Different concentrations of Salicylic acid (2 %, 5 %, and 10 %) are incorporated in a microemulsion base, composed of Isopropyl myristate, water, and Tween 80: Polyethylene glycol (in the ratio of 15:1). Microscopic examination, percent transmittance, pH, specific gravity, rheological properties, and accelerated stability studies are performed. The data showed that the addition of Salicylic acid is markedly affected the physical properties of the base. All systems are not affected by accelerated stability tests (67).

Khandpur et al., (2014) performed a prospective randomized open-label controlled trial to compare the efficacy and safety of topical application of coal tar-Salicylic acid ointment with Calcipotriol/Betamethasone dipropionate ointment applied once at night for 12 weeks for the treatment of limited chronic plaque psoriasis. Topical nightly application of coal tar-Salicylic acid ointment leads to an initial and rapid reduction in disease severity (68).

Raddadi et al., (2011) reported that Salicylic acid is the most widely used keratolytic agent. It softens the scaly layers of skin and eases their removal. It is applied to palms, soles, and scalp in concentrations of 2–10 %. Salicylic acid is especially useful in combination with corticosteroids to enhance penetration and improve clinical efficacy (69).

Making Cosmetics Inc., (2015) reported that one of the significant properties of Salicylic acid is its ability to remove skin cells of the most upper layer of the skin (stratum corneum). Salicylic acid has a concentration-dependent keratolytic effect. The concentration of 10–15 % of Salicylic acid shows a keratolytic effect after 2 or 3 days of application. Hence, Salicylic acid is widely used besides removing old cells and horny debris from the skin. The keratolysis also has the advantage that it facilitates the penetration of the other active ingredients into the skin. Salicylic acid is therefore often added to skin care products that contain active ingredients to increase their absorption.
and efficacy. It is a significant ingredient for peeling, exfoliation, or abrasion of the skin (70).

**Abbott et al., (2013)** prepared topical skin treatment formulation containing Salicylic acid or a derivative thereof, dissolved in a solvent system comprising dimethyl isosorbide, a C1–C9 alkyl salicylate, and a glyceryl fatty acid ester. The solvent system may also comprise an alcohol, a polyoxalkylene-based solvent, and a C1–C4 alkyl glucose ester. The formulation may be used in the treatment of acne. The solvent system improves the targeted delivery of the Salicylic acid or derivative to relevant sites on the skin (71).

**Combrinck et al., (2014)** revealed that if Salicylic acid is incorporated into the oil phase of the emulsions, an increase in emulsion droplet charge could negatively affect the release of Salicylic acid from the resulting emulsions. Contrary, positively charged emulsion droplets are found to enhance dermal and transdermal delivery of Salicylic acid from emulsions. It is hypothesized that complex electrostatic formation between the emulsifier and Salicylic acid could affect its release, whereas the electrostatic interaction between the emulsion droplets and skin could influence the dermal/transdermal delivery of Salicylic acid (72).

### 1.1.4 Review of Literature Regarding Ciprofloxacin

**Vali et al., (2009)** evaluated the efficacy and safety of topical Ciprofloxacin solution by comparing it with topical Erythromycin solution by single-blind clinical trial. Total, 100 patients with mild to moderate acne are enrolled. The patients are randomly treated with topical application of 0.3 % Ciprofloxacin or 4 % Erythromycin solutions for 6 week period and are visited every 2 weeks. Acne severity index is calculated in each visit and recorded. Reduction of pustules is more significant in Ciprofloxacin treatment group after 4 weeks. The results of this study indicated that topical solutions of Erythromycin and Ciprofloxacin are useful in treating mild to moderate acne vulgaris and both are well-tolerated by the patients. Ciprofloxacin solution produced a more significant reduction in pustule counts and acne severity index, during 6 weeks period of twice-daily application. This novel modality may have an
important potential role in rotational topical therapy of inflammatory acne lesions (12).

**Alcon Canada Inc, (2015)** reported that bactericidal action of Ciprofloxacin is due to inhibition of DNA gyrase enzyme, which is required for the synthesis of bacterial DNA (13).

**Spooner et al., (2011)** reported that pharmacokinetic-pharmacodynamics parameters are potential for bacterial eradication with antimicrobial therapy. Bactericidal activity can be time-dependent or concentration-dependent. Ciprofloxacin exhibit concentration-dependent bacterial killing (73).

**Tehler et al., (2013)** reported that esterification is used for a simultaneous increment of solubility and permeability of Ciprofloxacin. It is a BCS class IV drug (low solubility and low permeability) with limited solid-state solubility. Molecular flexibility is increased to disturb the crystal lattice, lower the melting point, and thereby improve the solubility, whereas lipophilicity is increased to enhance the intestinal permeability. These structural changes resulted in BCS class I analog (high solubility and high permeability) emphasizing that pure medicinal chemistry may improve both these properties (74).

**Rokade et al., (2015)** developed Ciprofloxacin-loaded topical preparation, to increase the local effect of Ciprofloxacin on the bacterially infected skin. Ciprofloxacin loaded topical formulation is optimized by changing the ratio of Span 60 and Lipotin A. Maximum entrapment efficiency and retention of Ciprofloxacin under *ex vivo* diffusion study was considered as dependent factors. The selected optimized formulation is subjected for *in vitro* and antibacterial activity studies and compared with the conventional Ciprofloxacin cream. The optimized batch of Ciprofloxacin containing topical formulation has shown 71 % of retention within 12 h and 46 % *in vitro* diffusion within 8 h (14).

**1.1.5 Review of Literature Regarding Chloramphenicol**

**Reddy et al., (2011)** reported that conventional ophthalmic formulations like solution, suspension, and ointment have many disadvantages like the pre-
corneal elimination of the drug(s) which result into poor bioavailability of the drug in the ocular cavity. The poor bioavailability may be overcome by the use of mucoadhesive in situ gel (installed as drops into the eye and undergo a sol-gel transition in the cul de sac). It has good mucoadhesion with ocular mucous layers. In vitro release of Chloramphenicol from in situ gel in simulated tear fluid is influenced by the properties and concentration of gelling agent (Chitosan and Carbomer 934). The longer pre-corneal residence time of Chloramphenicol has enhanced bioavailability. Significant reduction in the total bacterial count is observed for tested organisms for in situ gel of Chloramphenicol than Chloramphenicol solution (control) (18).

Iwalokun et al., (2011) reported that conjunctivitis is a red-eye condition with infections associated with transferable R plasmids of bacteria and has sensitive to Chloramphenicol, Ampicillin, and Streptomycin (75).

Flores-Paez et al., (2015) reported that Staphylococcus epidermis is a common commensal of the healthy conjunctiva, and it can cause conjunctivitis. Healthy conjunctiva isolates are more resistant to antibiotics than those with ocular infection. Ocular infection isolates have not developed resistance to Chloramphenicol, so it is recommended in ocular infections (16).

Hi-Media lab, (2015) reported that Chloramphenicol is a prototypical broad-spectrum antibiotic isolated from Streptomyces venezuelae. It acts by inhibiting protein synthesis at the prokaryotic ribosomal level. It binds to 50S ribosomal subunit and prevents association of aminoacyl-t-RNA with the ribosome. It exerts a bactericidal effect on gram-positive, gram-negative bacteria, and anaerobes. Chloramphenicol can exert bacteriostatic effect when used at high concentration or against highly sensitive organisms (76).

1.1.6 Drug Profile

1.1.6.1 Salicylic Acid (8)

Name of Drug : Salicylic acid
### Structure

![Structure of 2-hydroxybenzoic acid](image)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IUPAC Name</strong></td>
<td>2-hydroxybenzoic acid</td>
</tr>
<tr>
<td><strong>Molecular Formula</strong></td>
<td>C7H6O3</td>
</tr>
<tr>
<td><strong>Molecular weight</strong></td>
<td>138.12 g/mol</td>
</tr>
<tr>
<td><strong>Category</strong></td>
<td>Keratolytic agent</td>
</tr>
<tr>
<td><strong>Description</strong></td>
<td>White/colorless, acicular crystals or powder.</td>
</tr>
<tr>
<td><strong>Solubility profile</strong></td>
<td>2.24 mg/g in water at 25 °C, 625 mg/g in Methanol. Soluble in ether, Carbon tetrachloride, Benzene, Propanol, Acetone, Turpentine oil, and Toluene.</td>
</tr>
<tr>
<td><strong>log p value</strong></td>
<td>2.26</td>
</tr>
<tr>
<td><strong>BCS Class</strong></td>
<td>I (High solubility and high permeability)</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>10 % solution has pH of 2.</td>
</tr>
<tr>
<td><strong>pKa</strong></td>
<td>2.97</td>
</tr>
<tr>
<td><strong>Specific gravity</strong></td>
<td>1.443 g/mL</td>
</tr>
<tr>
<td><strong>Viscosity</strong></td>
<td>1.45 cP</td>
</tr>
<tr>
<td><strong>Minimum inhibitory concentration (MIC)</strong></td>
<td>8.9–22.33 mg/mL for <em>candida albicans</em></td>
</tr>
</tbody>
</table>

### 1.1.6.2 Ciprofloxacin (77)

**Name of Drug** : Ciprofloxacin

**IUPAC Name** : L-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-
7-(piperazin-1-yl) quinoline-3-carboxylic acid

Formula : C_{17}H_{18}FN_{3}O_{3}

Structure :

Molecular weight : 331.34 g/mol

Category : Concentration-dependent bactericidal

Description : A white to pale yellow, crystalline powder

Solubility profile : In DMSO < 1 mg/mL at 25 °C, 31 mg/g in Methanol, in Ethanol < 1 mg/mL at 25 °C, and insoluble in water.

log p value : 2.3

BCS Class : IV (Low solubility and low permeability) (74)

Density : 1.5 g/mL

pH : 3–4.5 (of 2.5 % solution)

MIC : MIC_{50}: 0.25 μg/mL; MIC_{90}: 0.5 μg/mL for *Propionobacterium acnes* (78); 0.25 μg/mL for *Staphylococcus epidermis*

Viscosity : 20 cP

pKa : 5.76

1.1.6.3 Chloramphenicol (19)

Name : Chloramphenicol
Introduction and Review of Literature

Formula: \( C_{11}H_{12}Cl_2N_2O_5 \)

Category: Bacteriostatic

Structure:

IUPAC Name: 2,2-dichloro-N-[(1R,2R)-2-hydroxy-1-(hydroxymethyl)-2-(4-nitrophenyl) ethyl]-acetamide

Molecular weight: 323.13 g/mol

Status: White to grey-white crystals or powder

Solubility: 2.5 mg/g soluble in water, 63 mg/g in Methanol

pH: 4.50–7.50

log p: 1.14

BCS Class: Class III (High solubility and low permeability)

Specific optical rotation: +18.5 to +20.5°

MIC: 8 \( \mu \)g/mL for Staphylococcus epidermis.

Density: 1.5 g/mL

pKa: 7.49

1.1.7 Excipients Profile

1.1.7.1 Neem oil (79)
<table>
<thead>
<tr>
<th><strong>Synonym</strong></th>
<th>Margosa oil</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family</strong></td>
<td>Meliaceae</td>
</tr>
<tr>
<td><strong>Biological Source</strong></td>
<td>The non-edible fixed oil obtained from fully matured seeds of <em>Azadirachta indica</em> Juss, Collected in late summer.</td>
</tr>
<tr>
<td><strong>Geographical Sources</strong></td>
<td>The plant found throughout India. Every portion has oil content, but seeds have a maximum of 20 % of the oil.</td>
</tr>
<tr>
<td><strong>Color</strong></td>
<td>Yellow</td>
</tr>
<tr>
<td><strong>Odor</strong></td>
<td>Bitter characteristics</td>
</tr>
<tr>
<td><strong>Taste</strong></td>
<td>Bitter</td>
</tr>
<tr>
<td><strong>Solubility</strong></td>
<td>Soluble in Ether and Chloroform.</td>
</tr>
<tr>
<td><strong>Specific gravity</strong></td>
<td>0.921 g/mL</td>
</tr>
<tr>
<td><strong>Refractive Index</strong></td>
<td>1.45</td>
</tr>
<tr>
<td><strong>Saponification Value</strong></td>
<td>203.9</td>
</tr>
<tr>
<td><strong>Moisture and insoluble Impurities</strong></td>
<td>0.17 % w/w</td>
</tr>
<tr>
<td><strong>Iodine Value</strong></td>
<td>71 Units</td>
</tr>
</tbody>
</table>
Acid Value : 3.8

Free Acid Value : 1.9

Peroxide Value : 1.2

Titer Value : 10–12 °C

Aflatoxin B₁ : < 2 ppm

Total aflatoxin (B₁, B₂, G₁, G₂) : < 4 ppm

Viscosity : 88 cSt; 88 cPs

Chemical constituents: Glycerides of saturated and unsaturated acids. Main fatty acids are Oleic acid (50 %), Stearic acid (20 %), Azadirachtin (0.2 %), sulfur-containing bitter compounds, Nimbin (0.3 %), Nimbidin, and Nimbidol. Unsaponified part contain Nimbosterol (0.03 %) and Salanine (0.5 %).

Use: Antibacterial, anti-parasitic, antifungal, antiprotozoal, and antiviral. Extensively used in hair fall, healing of wounds, diuretic, spermicidal, anti-arthritic, antidiabetes, acts on all kinds of skin disorders, anti-malarial action, good results in diseases like gonorrhea and syphilis. It works as an immune-boosting agent.

1.1.7.2 Isopropyl Myristate (80)

Non-proprietary Name : Tetradecanoic acid, 1-methyl ethyl ester

Specific Gravity : 0.864 g/mL
### Chemical Formula

CH$_3$(CH$_2$)$_{12}$COOCH(CH$_3$)$_2$

### Molecular Weight

270.45 g/mol

### CAS #

110-27-0

### Potential Acute Health Effects

Hazardous in case of eye contact (irritant), of ingestion. Slightly hazardous in case of skin contact (irritant, permeator), or inhalation. Do not use with an eye ointment.

### Serious Skin Contact

Not available

### Storage

Keep container dry. Keep in a cool place. Ground all equipment containing material. Keep container tightly closed.

### Incompatibility

Not available

### Federal and State Regulations

TSCA 8(b) inventory.

### HMIS

Health Hazard: 2, Fire Hazard: 1, Reactivity: 0, Personal Protection: j

### National Fire Protection Association (USA)

Health: 2, Flammability: 1, Reactivity: 0

### Viscosity

7 cPs

### 1.1.7.3 Olive oil (81)

### Synonym

Vegetable oil

### CAS #

8001-25-0
Chemical Name: Triglycerides of fatty acids

TSCA: TSCA 8(b) inventory.

Precaution: Not irritant to eye and skin

Specific Gravity: 0.93 g/mL

Color: Greenish-yellow

Iodine value: 79–88

Saponification value: 190–195

Chemical constituents: Triglycerides of Olein, Palmitin, and linolein.

Storage: Keep container tightly closed in a cool and well-ventilated area. Do not store > 23 °C (73.4 °F).

Taste: Pleasant, delicate flavor; faintly acrid after taste (slight)

Federal and State Regulations: Connecticut carcinogen reporting list: TSCA 8(b) inventory.

Other Regulations: The European Inventory of Existing Commercial Chemical Substances (EINECS).

HMIS: Health Hazard: 1

Viscosity: 110 cp

1.1.7.4 Mogra oil (82)

Specific Gravity: 0.959 g/mL

Precaution: Not irritant to skin
### Peppermint Oil

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
<td>Essential oil</td>
</tr>
<tr>
<td><strong>Functional Category</strong></td>
<td>Oil</td>
</tr>
<tr>
<td><strong>CAS #</strong></td>
<td>8022-96-6</td>
</tr>
<tr>
<td><strong>TSCA and Federal and State Regulations</strong></td>
<td>TSCA 8(b) inventory.</td>
</tr>
<tr>
<td><strong>Skin Contact</strong></td>
<td>No known effect on skin contact.</td>
</tr>
<tr>
<td><strong>Viscosity</strong></td>
<td>40 cP</td>
</tr>
</tbody>
</table>

#### 1.1.7.5 Peppermint oil (83)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAS #</strong></td>
<td>8006-90-4</td>
</tr>
<tr>
<td><strong>TSCA</strong></td>
<td>TSCA 8(b) inventory.</td>
</tr>
<tr>
<td><strong>Specific Gravity</strong></td>
<td>0.898 g/mL</td>
</tr>
<tr>
<td><strong>Odor</strong></td>
<td>Characteristic, minty.</td>
</tr>
<tr>
<td><strong>Taste</strong></td>
<td>Pungent</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>Optical Rotation</strong></td>
<td>16–30° at 25 °C</td>
</tr>
<tr>
<td><strong>Refractive Index</strong></td>
<td>1.459–1.465</td>
</tr>
<tr>
<td><strong>Chemical Constituents</strong></td>
<td>Menthol (7–40.7 %) and Menthone (23.4 %)</td>
</tr>
<tr>
<td></td>
<td><em>Piperita</em> contains 9.8–26.2 % Menthol.</td>
</tr>
<tr>
<td><strong>Effect on Eye</strong></td>
<td>No signs of eye irritation are observed if</td>
</tr>
<tr>
<td></td>
<td>Menthol is administered at 0.025–0.1 %</td>
</tr>
<tr>
<td></td>
<td>concentrations. Moreover,</td>
</tr>
</tbody>
</table>
no substantial toxic reactions are observed in electrophysiological, corneal hydration level, or histological examinations after the addition of 0.1 % Menthol (85, 86).

Federal and State Regulations

Color : Colorless to light yellow

Other : OSHA: Hazardous by definition of Hazard Communication Regulations

Density : 0.898 g/mL

Viscosity : 4 cp

1.1.7.6 PEG-20 Sorbitan Monolaurate (87, 88)

Trade name : Tween® 20

Synonym : Polysorbate 20, polyoxyethylene sorbitan monolaurate

Molecular formula : C_{58}H_{114}O_{26}

Molecular weight : 1128 g/mol

CAS No : 9005-64-5

Appearance : Clear, yellow to yellow-green viscous liquid

Boiling point : > 100 °C

Viscosity : 370–430 cps (at 25 °C)

pH of 1 % aqueous solution : 5–7
Refractive index : 1.4685
Specific gravity : 1.1 g/mL
HLB : 16.7
Critical micelle concentration value : 60 mg/L
Structure : Polyoxyethylene sorbitol ester
Nature : Nonionic
Miscibility : With water, alcohol, dioxane, ethyl acetate. Practically insoluble in liquid paraffin and fixed oils.
Functional Category : Dispersing agent; emulsifying agent; nonionic surfactant; solubilizing agent; suspending agent; wetting agent.
Odor : Characteristic
Taste : Slight bitter
Acid value (%) : 2.0
Hydroxyl value : 96–108
Moisture content : 3.0
Saponification value : 40–50
Regulatory Status : USFDA IIG Database (intramuscular, intravenous, oral, and topical preparations), generally regarded as nontoxic and nonirritant materials.
Viscosity : 400 cP

1.1.7.7 Acrysol™ K-150 (89)
Non-propitiatory Name: Acrysol™

US DMF Registration No.: 23259

Chemical name: Propylene glycol-polyoxyl 40-hydrogenated castor oil

Color: White to pale yellow

Physical form: Viscous liquid

Odor: Odorless

Taste: Tasteless

Miscibility: At elevated temperature, it forms clear mixtures with fatty acids and fatty alcohols. It forms a clear solution in water, Ethanol, 2-Propanol, n-Propanol, Ethyl acetate, Chloroform, Carbon tetrachloride, and Toluene.

Effect of Temperature: Stable and does not turn rancid unless subjected to excessive heat. Before using in any application, Acrysol™ K-150 must be heated up to 50–60 °C. Stable over a broad temperature range and pH independent.

Typical applications: It improves the solubility of poorly soluble drugs.

Emulsifier: Acrysol™ range is an excellent versatile emulsifying agent. It emulsifies major hydrophobic substances like fatty acids, fatty alcohols, and mineral oil.
**Toxicity**

Acute and chronic toxicity test in animals has shown that Acrysol™ grades are substantially non-toxic and non-irritant material.

**Shelf-life**

2-years from the date of manufacturing in sound condition.

**Specification**

Confirms to USP/NF/ EP specification

**Sensitization**

Solutions of 20 % and 50 % concentration in Acetone were brushed 10-times on the skin of Guinea pigs. They did not cause any sensitization of the skin.

**Compatibility**

With skin and mucous membranes: Swab tests have demonstrated that Polyoxyl 40 hydrogenated Castor oil is compatible with human skin.

**Advantages**

Versatility, tasteless, colorless and transparent, reduces consumption, stable over a wide temperature range, self-shining, highly hydrophilic, improve foam stability, pH-independent, elegant, smooth and luxurious feeling, biodegradable, and eco-friendly.

**Congealing temperature**

200–300 °C

**Hydroxyl value**

60–80

**Iodine Value**

Not more than 2 %

**Saponification Value**

45–69 %
pH : 6–7 (10 % aqueous Solution)

Refractive index : 1.45 + 0.004 (at 20 °C)

Water : Not more than 3 %

Residue on Ignition : Not more than 0.3 %

Heavy Metals : Not more than 0.001 %

Acid Value : Not more than 2 %

HLB Value : 12–16

Viscosity : 20–40 cp

1.1.7.8 Polyethylene Glycol-400 (88)

Non-propitiatory name : BP: Macrogols, JP: Macrogol 400, PhEur: Macrogola

Synonym : Carbowax; CarbowaxSentry; Lipoxol; Lutrol E; PEG-400; Pluriol E

CAS Reg. No. : 25322-68-3

Chemical Name : \( \alpha \cdot \text{Hydro-}\omega\cdot \text{hydroxy} \text{poly (oxy-1,2-ethanediyl)} \)

Empirical Formula : \( \text{HOCH}_2\text{CH}_2\text{OCH}_2\cdot 7\text{CH}_2\text{OH} \)
Molecular Weight: 380–400 g/mol

Structural Formula:

```
H
(H2O)nC
H
```

Functional category:
Ointment base, plasticizer, solvent, suppository base, tablet, and capsule lubricant.

Density: 1.11–1.14 g/mL at 25 °C

Refractive Index: $n_D^25$: 1.465

Flash Point: 238 °C

Solubility: Soluble in acetone, alcohols, benzene, and glycerin.

Surface Tension: Approximately 44 mN/m (44 dynes/cm)

Viscosity: 105–130 cp

Applications: Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral and rectal preparations. It has been used experimentally in biodegradable polymeric matrices used in controlled-release systems. They do not readily penetrate the skin, although the polyethylene glycols are water-soluble and are easily removed from the skin by washing, making them useful as ointment bases. In film coatings, solid grades of Polyethylene glycol can be used alone or can be used as hydrophilic polishing materials.
**Stability and Storage**

Stable, slightly hygroscopic material. Chemically resistant to alkalis and salt solutions, although more sensitive to acidic materials than cellulose esters.

**Regulatory Status**

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA IIG (oral capsules, suspensions, and tablets; topical emulsions and vaginal preparations). Included in nonparenteral medicines licensed in Europe. Included in the Canadian List of Acceptable Non-Medicinal Ingredients.

**Handling Precaution**

It is essential to prevent deterioration during storage.

**IIG as per USFDA**

Up to 20 g/kg body weight for topical gel (90)

**Viscosity**

105–130 cp

**HLB**

11.6

### 1.1.7.9 Carbomer 934 (88)

**Non-Proprietary name**

Carbomers

**Synonym**

Acrypol; Carbomera.

**Chemical name**

Carboxy polymethylene

**CAS No.**

9007-16-3
Structure

USP limit: Previously dried in vacuum at 80 °C for 1 h contains not less than 56 % and not more than 68 % of Carboxylic acid (-COOH) gr (91).

Use: Emulsifying agent, suspending agent, tablet binder, viscosity increasing agent, and a gelling agent.

Functional Category: Gelling agent.

Description: White colored fluffy, acidic and hygroscopic powder with slight characteristic odor.

Solubility: Soluble in water and after neutralization of Ethanol (95 %) and Glycerin.

Viscosity: 0.5 % neutralized aqueous dispersion has 35,000 cPs

Stability: Stable through the hygroscopic material may be heated at a temperature below 104 °C for up to 2 h without affecting their thickening efficiency.

Storage: Dry powder forms do not support the growth of molds and fungi, but aqueous dispersion is very susceptible to the microorganism.

Safety: It is regarded as non-toxic and non-irritant material.
Regulatory Status: GRAS listed, FDA IIG, included in Canadian list of Acceptable Non-Medicinal Ingredients, included in nonparenteral medicines licensed in Europe.

Concentration used: 0.5–2 % for topical gel.

IIG as per USFDA: Up to 2 % for topical gel (92).

Density: 0.3 g/mL

pH: 2.5–4.

1.1.7.10 Triethanolamine (93)

Non-propitiatory Name: TEA

CAS No.: 102-71-6

Functional Category: pH adjusting Agent

Chemical Structure: $N(CH_2CH_2OH)_3$

Formula: $C_6H_{15}NO_3$

Concentration Used: Generally, 1–2 % (for topical gel).

Sensitization: Negative results of sensitization on Guinea pig

LD₅₀: 2 g/kg [Dermal (rabbit)].

Color: Light yellow.

Odor: Amine-like.

Physical Status: Liquid.

Specific gravity: 1.12 g/mL

pH: 10.5–20 °C.

1.1.7.11 Propylene Glycol (42, 92, 94, 95)

Non-propitiatory Name: Propylene glycol (BP/JP/PhEur/USP).

Synonyms: 1,2-Dihydroxy propane, E1520; 2-Hydroxypropanol, Methyl ethylene alcohol, Propane-1,2-diol.

CAS No.: 57-55-6.

Empirical Formula: C₃H₈O₂
Molecular Weight: 76.09 g/mol.

Used strength: 5–10 %.

Description: Clear, colorless, viscous, partially odorless, liquid with a sweet or slightly acrid taste resembling that of glycerin.

Auto Initiation: 3718 °C

Boiling point: 1888 °C

Density: 1.035–1.037 g/mL at 20 °C

Melting Point: 598 °C

Osmolarity: A 2 % v/v aqueous solution is isotonic with serum.

Solubility: Miscible with Acetone, Chloroform, 95 % Ethanol, Glycerin, water, some of the essential oils, etc.

Surface tension: 40.1 m/N/m (dyn/Sec) at 25.8 °C

Viscosity: 58.1 cPs

Stability and Storage Conditions: At cool temperature, Polyethylene glycol is stable in a well-closed container, but at high temperature, it tends to oxidize giving rise to a product such as Propionaldehyde, Lactic acid, Pyruvic acid, and Acetic acid. Polyethylene glycol is chemically stable when mixed with Ethanol (95 %), Glycerin or water.

Safety: Used in a wide variety of pharmaceutical formulations, is regarded as
relatively non-toxic material, it is also used extensively in food and cosmetics. Probably a consequence of its metabolism and excretion. Less toxic among other glycols. \( \text{LD}_{50} \) of dermal in the rabbit is 2 g/kg. It did not cause allergic skin reaction in humans.

Surface tension : 40.1 m/N/m (dyn/s) at 25.8 °C

Viscosity : 58.1 cPs


Applications: Widely used as a solvent, plasticizer, extractor, emulsifier, and preservative in a wide variety of parenteral and non-parenteral pharmaceutical formulations.

1.1.7.12 Oleic Acid (88)

Synonyms : Acidum oleicum; Crodolene; Crossential 094; Elaic acid; Emersol; Glycon; Groco; Hy-Phi; Industrene; Metaupon; Neo-Fat; Cis-9-octadecenoic acid; 9,10-Octadecenoic acid; Oleinic acid; Priolene.

Chemical Name : (Z)-9-Octadecenoic acid

CAS Registry Number : 112-80-1
**Empirical Formula**: \( \text{C}_{18}\text{H}_{34}\text{O}_{2} \)

**Molecular weight**: 282.47

**Category**: Skin penetrant

**Description**: A yellowish to pale brown, oily liquid with a characteristic lard-like odor and taste.

**pH**: 4.4

**Density**: 0.895 g/mL

**Viscosity**: 26 cP at 25 \(^{\circ}\)C

**Chemical constituents**: Usually, 7–12 % saturated acids, such as Stearic and Palmitic acid, together with other unsaturated acids, such as Linoleic acid.

**Safety**: Moderate skin irritant, not used in eye preparations.

**Regulatory Status**: GRAS listed, USFDA, licensed in the UK. Included in the Canadian list of acceptable non-medicinal ingredients.

**1.1.7.13 Sepineo™ P 600 (96, 97)**

**Chemical Name**: Acrylamide/Sodium Acryloyl dimethyl Taurate Copolymer / Isohexadecane and Polysorbate 80
Introduction and Review of Literature

CAS NO. : 38193-60-1/93685-80-04/9005-65-6

US DMF No. : 21266

Specification : Latex white liquid

Functional category : Gelling agent (three in one polymer for topical application)

Flow behavior : Pseudoplastic

Regulatory Status : DMF-FDA(USA), IPEC (GMP), IIG (USA)

Thickening range : 2–12 pH for topical gel.

IIG as per USFDA : 0.5–5 %

Odor : Faint

pH : 5–7 (2 % w/w solution)

Density : 1.1 g/mL at 20 °C

Log p : > 7 of Isohexadecane

LD50 Dermal : 3000 mg/kg for rabbit (Isohexadecane)

Shelf-life : 2 years
### 1.1.7.14 Xanthan Gum (81)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS Reg No</td>
<td>11138-66-2</td>
</tr>
<tr>
<td>Formula</td>
<td>((C_{35}H_{49}O_{29})_n)</td>
</tr>
<tr>
<td>Synonym</td>
<td>Corn sugar gum; <em>Keldent</em>; <em>Keltrol</em>; <em>Rhodicare S</em>; <em>Rhodigel</em>; <em>Vanzan NF</em>; Xanthani gummi; <em>Xantural</em>.</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>Approximately (1 \times 10^6)</td>
</tr>
<tr>
<td>pH</td>
<td>6–8</td>
</tr>
<tr>
<td>Specific Gravity</td>
<td>1.6 g/mL at 25 °C</td>
</tr>
<tr>
<td>Incompatibilities</td>
<td>Anionic and amphoteric surfactants at concentrations above 15 % w/v cause precipitation of Xanthan gum.</td>
</tr>
<tr>
<td>Safety</td>
<td>Regarded as nontoxic and nonirritant at the levels employed as a pharmaceutical excipient. No eye or skin irritation has been observed in rabbits, and no skin allergy has been observed in Guinea pigs following skin exposure.</td>
</tr>
<tr>
<td>Regulatory Status</td>
<td>GRAS listed.</td>
</tr>
</tbody>
</table>

Accepted for use as a food additive in Europe.

Included in the FDA Inactive Ingredients Database.

Included in nonparenteral medicines licensed in the UK.

Included in the Canadian List of Acceptable Non-
medicinal Ingredients.

EINECS No. : 234-394-2

PubChem ID : 7107

1.1.7.15 Sodium Lauryl Sulfate (81)

Non-proprietary Names : Sodium Lauryl Sulphate, Sodium Lauryl Sulfate

Synonyms : Dodecyl alcohol hydrogen sulfate, sodium salt; Dodecyl sodium sulfate; Dodecyl sulfate sodium salt; Elfan 240; lauryl sodium sulfate; Lauryl sulfate, sodium salt; Mono dodecyl sodium sulfate; Natrii laurilsulfas; Sodium dodecyl sulfate; Sodium n-dodecyl sulfate; Sodium laurilsulfate; Sodium monododecyl sulfate; Sodium monolauryl sulfate; SDS; SLS; Sulfuric acid monododecyl ester, sodium salt; Texapon K12P

Chemical Name : Sulfuric acid monododecyl ester sodium salt (1:1)

CAS Reg. No : 151-21-3

Formula : \( C_{12}H_{25}NaO_4S \)

Molecular Weight : 288.38 g/mol

Functional Category : Anionic skin penetrant
Description: White or cream to pale yellow colored crystals, flakes, or powder having a smooth feel, a soapy, bitter taste, the faint odor of fatty substances.

pH: 7–9.5 (1 % w/v aqueous solution).

Antimicrobial activity: Against gram-positive bacteria, it potentiates the fungicidal activity of certain substances.

Density: 1.07 g/mL at 20 °C

HLB value: 40

Safety: Moderately toxic material with acute toxic effects including irritation to the skin, eyes, mucous membranes, upper respiratory tract, and stomach.

Regulatory Status: GRAS listed. Included in the FDA II G Database, included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.