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Recent update on nanoemulgel as topical drug delivery system

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ABSTRACT:

Being an emerging transdermal delivery tool, nanoemulgel, has proved to show surprising upshots for the lipophilic drugs over other formulations. This lipophilic nature of majority of the newer drugs developed in this modern era resulting in poor oral bioavailability, erratic absorption and pharmacokinetic variations. Therefore, this novel transdermal delivery system has been proved to be advantageous over other oral and/or topical drug delivery to avoid such disturbances. These nanoemulgels are basically oil-in-water nanoemulsions gelled with the use of some gelling agent in it. This gel phase in the formulation is non-greasy which favors user compliance and stabilize the formulation through reduction in surface as well as interfacial tension. Simultaneously, it can be targeted more specifically to the site of action and can avoid first pass metabolism and relieve the user from gastric/systemic incompatibilities. This brief review is focused on nanoemulgel as a better topical drug delivery system including its components screening, formulation method and recent pharmacokinetic and pharmacodynamic advancement in research studies carried out by the scientists all over the world. Therefore, at the end of this survey it could be inferred that nanoemulgel can be a better and effective drug delivery tool for the topical system.

Keywords: Nanoemulgel; Nanoemulsion; Transdermal drug delivery; Pharmacokinetic improvement.
1. Introduction

Since the dawn in pharmaceutical culture in Mesopotamia (2600 B.C.) by the use of water, and plant for the treatment of ailment, pharmacists are able to develop the era of modern dosing systems [1]. Researches in this field have introduced several routes of administration to deliver the developed modern dosage forms. The dosage forms are mostly dependent on the physicochemical characteristics of the active compound. Recent trend of synthesis drug development or during high throughput screening leads towards development of lipophilic active pharmaceutical agents [2]. Recent statistical reports on poor aqueous solubility of new chemical entities (NCE) (70%) [3] has crossed the initial report of around 40% NCE with poor solubility [4–9]. Lipophilic characteristics of the newly developed drug molecules manifest the problems like poor oral bioavailability, erratic absorption, intra- and inter-subject pharmacokinetic variations and lack of dose proportionality [10]. To overcome those issues to focus on solubility enhancement, formulation approach is a continuous developing process. Different strategies such as physical modification, chemical modification and formulation development (Figure 1) can be used to improve the solubility of poorly soluble drugs. There have been numerous formulation approaches to improve the solubility of poorly aqueous soluble drugs such as particle size reduction to deliver through nanocarrier system, crystal engineering, amorphous formulation [11–15], several lipid formulations approaches [16], etc. Newer lipid formulation techniques, viz: incorporation of lipophilic component in inert lipid vehicle [17,18], formation of microemulsion or nanoemulsions [19], self-emulsifying formulations, liposomes, solid lipid nanoparticles or lipid nanocarriers [20–22] are becoming increasingly popular to overcome these problems of lipophilic properties of compounds. Consequently, several route of administration have been explored to deliver those formulations based on its distinct advantages and disadvantages on target site, severity of disease, patients’ age and condition, available dosage form and finally for the compliance of the users.

Oral route is the most preferred route anchored in patient compliance, however, oral administration is more prone to result in hepatic first pass metabolism, leading towards requirement of higher dose [23,24]. Further, gastric irritation is the major limitations for the presence of surfactants in the lipid based formulations [25], simultaneously the distribution of drug throughout the body can lead to unavoidable side effects. Hence, to stay away from such unacceptable issues, the non-invasive, non-paining, non-irritating topical delivery of
formulation is an alternate way associated with several advantages such as delivery of drug to specific site of action with reduced systemic toxicity, avoidance of first pass metabolism and gastric irritation, increasing release rate of drug from formulation to improve percutaneous absorption and sometime topical application related to increase bioavailability with sustained release profile [26,27].

Besides its advantages described, traditional transdermal formulations, viz: ointments, creams, lotions are in accord with many disadvantages such as sticky nature, lack of spreadibility, stability issue, etc., ultimately leading to patient incompliance. Modernization of transdermal delivery by the formulation revealed transparent gel and emulgel with greater patient compliance and improved efficacy. Thus, these formulations are gaining interest both in cosmetics industries, as well as in pharmaceutical industries. In spite of lots of advantages of gel and emulgel formulations, delivery of hydrophobic drug still remains a big hurdle to cross over. Moreover, skin penetration through stratum corneum is also a great concern to the researchers for the systemic activity of the transdermal delivery. Literatures suggest that nanosized topical formulations can enhance permeability of the active moiety by disrupting the lipid bilayer as evident from the distinct void and empty spaces in the nanoemulsion treated skin samples [28] and extent retention of the drug at the site of action [29,30]. Nanoemulsion bears much hope being isotropic, transparent (or translucent) heterogeneous mixture composed of two media (oil and aqueous), one phase is dispersed in another and stabilized by an interfacial film of surfactant molecules [31]. Studies suggested that nanoemulsions have a higher drug solubilization capacity than simple micellar solutions, and their thermodynamic stability offers advantages over unstable dispersions, such as emulsions and suspensions, because they can be manufactured with little energy input (heat or mixing) and have a longer shelf-life [18]. Regardless of lots of advantages of nanoemulsion, topical application is limited due to its low viscosity and spreadibility [32]. Researchers have solved the problems associated with nanoemulsion for transdermal delivery through a simple conversion of nanoemulsion to nanoemulgel. Nanoemulgels are nanoemulsion, either of oil-in-water (o/w) or water-in-oil (w/o) type which further convert to nanoemulgel by using gelling agent [33]. Nanoemulgel possesses gel characteristic with improved nanoemulsion properties for transdermal application. Other advantages of nanoemulgel include its low skin irritation, increase permeability, and high drug-loading capacity for topical delivery when compared with the other carriers such as microemulsions, liposomes or solid lipid nanoparticles [34–36]. This colloidal delivery system can be utilized to incorporate drug compounds to target on bioavailability
improvement, increase stability plateau and reducing their side effects [37]. Nanoemulsion ensures adequate localization and dispersion of the drug by adequate percutaneous absorption within the skin to enhance its local efficacy and/or through the skin to the circulation to polish its systemic effect and even can cross the rigid blood-brain-barrier to offer added advantages in CNS activity [38].

Hanging on the researcher’s interest, patient acceptance and interesting research outcomes in the field of pharmaceutical formulation development, study on nanoemulgel focuses on development of vast number of delivery system viz: transdermal, dental, vaginal, ocular, nose to brain nanoemulgel for treatment of various local as well as systemic ailments [39–45]. There are a very few review articles available in the literature mainly focusing on formulation overview and penetration aspects of emulgel [46], characterization of the nanoemulgel [47], current market products on nanoemulgels and its advantages [48] and delivery of antifungal agents through nanoemulgel delivery [27]. Present article is an extensive review covering components screening for nanoemulgel formulation combined with its formulation overview and pharmacokinetic and pharmacodynamic parameters of the published research works on nanoemulgel with different pharmaceutical products. Therefore, the aim of the present study is to give an overview on the selection criteria of the basic component for nanoemulgel and its positive/negative role in experimental results on pharmacokinetics, pharmacodynamics, and safety of the drug. Connecting section of the article will reveal the components and selection criteria for the achievement of targeted objective.

2. Formulation components consideration

Either of o/w or w/o nanoemulsion is composed of an oil phase and aqueous phase, where the tiny dispersed phase is enervated by a thin layer of surfactant, which sometimes augmented by the presence of co-surfactant. Overview of oil selection strategies to utilize several inherent properties of the incorporating oil has been apprehended in the connecting section.

2.1. Oil selection

One of the important components of the nanoemulgel is the lipid component, i.e., oil. There is requirement of several investigations to select an appropriate oil phase based on viscosity, permeability, and stability of the formulated nanoemulsion. Sometimes selection of
The oil phase is also dependent on utilization of the medicinal property of some natural oils [49]. Based on the source of the oil, it has been observed that vegetable oils (of long-chain fatty acids) had poor emulsification properties, therefore result in unstable nanoemulsion [50,51]. On the other hand, emulsification property was found to be better when the oil was with less hydrophobic property [52]. Contrary, increased hydrophobicity affects the solubility of the lipophilic drugs in it. Therefore, selection of appropriate oil is a critical step in formulation development. A selection strategy of an appropriate oil phase for a nanoemulgel to plan is represented in Figure 2.

Oleic acid, a biocompatible and biodegradable omega-nine fatty acid, available from many vegetables source and animal products, is widely used as an oil phase in nanoemulgel formulation not only due to its high solubilization properties, but also for its well-known percutaneous absorption enhancer property [53] and formulation stabilization property [54,55]. Additionally, reach antioxidants in oleic acid known to strengthen the cell membrane integrity, helps in replacing cells and tissues damage. Due to presence of such advantageous properties, this oleic acid has been used as a permeation enhancer for many drugs [54], for the development of topical nanoemulgel with piroxicam [55]. Dhawan and its group reported that there is improved permeation rate with increased percentage of oleic acid in the formulation. Further, enhancement of ketoprofen permeability was observed [54] by increasing oleic acid from 3% to 6%. On analyzing, it has been observed that lipid fluidization and lipid phase separation are the two mechanism by which oleic acid increases the permeability and easily permeate within lipid bilayers of the stratum corneum [56,57]. However, high concentration of oleic acid could decrease the permeation rate which might be due to aggregation of oil [55]. Besides, incorporation of oleic acid in diclofenac diethyl amine nanoemulgel could be one of the possible reasons for the increased cumulative percentage permeated through stratum corneum [58].

Thus, oils from natural sources have proved to contain additional medicinal value(s) and now-a-days scientists all over the world are more focused to utilize such supplementary benefit in therapeutic effect. Another oil from emu bird, emu oil also gained interest in pharmaceutical industry for its anti-inflammatory, analgesic, anesthetic, antipruritic and antioxidant properties [59]. Such important therapeutic activities of emu oil were utilized by the Jeengar and team. They manufactured curcumin nanoemulgel with improved permeability in the ailment of joint synovium [59]. Parenteral medicaments are also gaining attention to
deliver through transdermal route with the utilization of its penetration enhancing properties to the site of action for a prolonged period. Excellent hypoglycemic activity of insulin had been reported by the researchers in experimental rabbits when it was delivered through percutaneous emulgel delivery [60]. Uses of emu oil is not only cornered in pharmaceutical industries, it is also gaining importance in cosmetic industries due to its moisturizing benefits to the skin [61]. Its’ resemblance to skin composition due its high percentage of unsaturated fatty acid with major percentage of oleic acid [62,63] further helps in penetration enhancement of drug through skin.

Furthermore, another natural oil – tea tree oil, is well known for their broad spectrum antimicrobial activity [64]. Thus, use of tea tree oil as a formulation ingredient can be beneficial in application on fungal and bacterial infection. The stable and thermo sensitive nanoemulgel of itraconazole, an azole antifungal agent, with tea tree oil was reported with synergistic effect against vaginal candidiasis [42]. Drug loading in tea tree oil was improved using organic solvent during nanoemulgel formulation development. Skin penetration of itraconazole was improved through nanoemulgel delivery, which might be due to the presence of nano sized droplet of tea tree oil and its major component terpinen-4-ol [65]. Instead of its various advantages, use of tea tree oil as a formulation component is limited for transdermal delivery due to its allergic properties [66,67]. Further evaluation revealed that, 1,8-cineole, a component of tea tree oil has known to cause skin irritation, provided its content should have ≥28% [66]. But we are fortunate enough to know that tea tree oil has only 15% 1,8-cineole. So whenever developing a formulation with tea tree oil as a component, judicious selection of tea tree oil concentration will be an important factor. Itraconazole nanoemulgel with tea tree oil did not produce any irritation potential and any sign of abnormality in histopathology study due to low percentage of tea tree oil (10% in nanoemulgel) [42]. Another nanoemulgel of synthetic trizole antifungal drug, fluconazole, has been reported by Pathak and team for topical application. They reported that ocular application of the nanoemulgel formulated with Capmul MCM as an oil phase due to its high solubilization potential for fluconazole, adequate water solubility and well tolerance to the eye [68,69].

Eugenol, a phenolic compound obtained from Eugenia aromatica, is well known for its analgesic, local anesthetic, anti-inflammatory, and antibacterial properties [70]. Srivatava and team had been utilized eugenol as an oil phase in ketoprofen nanoemulgel formulation
They observed a supra-additive synergistic antibacterial activity of ketoprofen in eugenol nanoemulgel formulation against *Staphylococcus aureus* and *Escherichia coli* which is due to the nano delivery of ketoprofen as well as due to presence of eugenol in formulation [70].

Occasionally, the target compound or the active ingredient was employed as an oil phase in nanoemulgel development. One of such component is *swieteniamacrophylla* nanoemulgel where *swieteniamacrophylla* is used as an oil phase. It has been revealed that the anti-inflammatory property of *swieteniamacrophylla* was higher when delivered through nanoemulgel formulation compared to its parent form [71].

As discussed earlier, the edible/vegetable oils are not frequently useful due to their poor ability to dissolve large quantity of lipophilic drugs and poor emulsification properties. Therefore, chemically modified oils, like medium-chain triglycerides or mono- or diglyceride are frequently used as an oil phase in formulation development to deliver poorly water soluble drugs [72]. Capryol 90 is one of such example with hydrophilic lipophilic balance of 5, due to its lipophilicity easily solubilize drugs with less polar area. Published literature revealed that the presence of the numerous advantageous properties, Capryol 90 has been used as an oil phase for the development of nanoemulsion for various lipophilic compounds to target improvement of their pharmacokinetic/pharmacodynamic properties [33,73].

Medium chain triglycerides are suitable for encapsulating drugs with log-P value ranging from 2 to 4 [74]. Labrafac is another example of medium-chain triglyceride used as fat phase in nanoemulsion preparation [75,76]. Among the available variety of it, Labrafac™ Lipophile WL1349 was used for the development of nanoemulgel for transangual delivery of ketoprofen [77]. An additional medium chain triglyceride Capmul MCM found to be widely used in pharmaceutical research. It has HLB value of 5 to 6, therefore, reported to have good solubility with water. It has also proven to be an appropriate oil phase for ocular nanoemulsion formulation due to its non-irritating properties on human eye [68]. A different medium chain triglyceride, Miglyol 812, is also preferred for ocular delivery through nanoemulgel formulation as it is too well tolerated with human eyes. In spite of the non-irritability property of Miglyol 812 for ocular delivery, use of it is limited due to less nanoemulsifying area in pseudoternery phase diagram which might be due to its higher molecular volume and smaller alkyl chain [78]. Nevertheless, suitable combination and composition with an appropriate surfactant might result a stable nanoformulation [79] for the
improvement of solubility of poorly water soluble drugs. In their research, Tayel et al. developed non-irritant ocular nanoemulgel of terbenafine hydrochloride with Miglyol 812 and achieved a thermodynamically stable, sustained released and improved bioavailable formulation [79].

2.2. Surfactant and co-surfactant selection

2.2.1. Surfactant

Surfactants are integral component of nanoemulsion system which is used to stabilize the thermodynamically unstable mixture of two immiscible liquids by reducing the interfacial tension between them and change the dispersion entropy. Safety, stability and high drug loading capacity along with good emulsification properties are the basic requirements for the surfactants integrated in nanoemulsion development, [51]. A suitable surfactant used in nanoemulsion formulation should be adsorbed rapidly onto the interface of the two immiscible phases leading to dramatically reduction of interfacial tension and prevents coalescence of the nano droplets [80].

Due to the presence of ionic nature, these stabilizing systems are classified into the following categories: cationic surfactant (amines and quaternary ammonium compounds, cetyl trimethyl ammonium bromide, lecithin, hexadecyl trimethyl ammonium bromide, dodecyl dimethyl ammonium bromide, etc.), anionic surfactant (containing carboxylate group, sodium bis-2-ethylhexylsulfosuccinate, sodium dodecyl sulfate), zwitterionic surfactant (phospholipid), and non-ionic surfactant (Capryol 90, Labrafil CS, Labrasol, Gelucire 44/14, 50/13, Cremophor RH 40, Cremophor EL, Imwitor 191, 742, 780 k, 928, 988 M, 2125 CS, Lauroglycol 90, PEG MW > 4000, Plurol Oleique CC 497, Poloxamer 124 and 188, Softigen 701, 767, Tween 20, Tween 60, and Tween 80, etc). Their working mechanism based on the repulsion force between nano droplets, because presence of similar ionic charge on the head of the surfactant molecule on the interface of the dispersed and continuous phase prevents aggregation of droplets leading to thermodynamically stable nanoemulsion [81].

There are various factors which governs the selection of surfactants. The first and most important feature is the associated toxicity of the surfactant used. Proper selection of surfactant is important due to large amount of surfactant may cause irritation to skin and GI tract when administered topically and orally, respectively. So it was advocated to incorporate minimum amount of surfactant in formulation. Another selection criteria include the HLB
value of the surfactant. Based on the hydrophilic-lipophilic balance (HLB) values of the available surfactants, they are classified as \( w/o \) emulsifying agent (HLB 3-8) and \( o/w \) emulsifying agent (HLB 8-16) [82,83]. Therefore, to develop an \( o/w \) nanoemulsion, HLB value of the selected surfactant should be greater than 10. Thus, in \( o/w \) emulsion, Tweens and Spans having HLB value more than 8 are used. Additionally, combination of Span 20 and Tween 20 contribute towards greater stability of the emulsions as compared with pure Tween or Span systems [84,85]. Conversely, to stabilize \( w/o \) emulsion, surfactants having HLB value less than 8 are used [86]. However, formation of stable nanoemulsion can be obtained from appropriate mixing of low and high HLB surfactants. On the similar concept, Noor El-Din et al. prepared water-in-diesel fuel nanoemulsion by using mixture of Tween 80 (HLB-15) and Span 80 (HLB-4.3) [87]. In such system, the hydrophilic and lipophilic emulsifiers are thought to align alongside each other imparting more rigidity and strength to the emulsifier film through hydrogen bonding and making nanoemulsion more stable. Several authors affirmed that surfactant mixtures could provide more stable emulsions with the minimum size of dispersed droplets than use of any one [88,89]. These surfactants improves stability of nanoemulsion by lowering the needed energy to formulate nanoemulsion [90,91].

An additional criteria of surfactant selection is the type and nature of surfactants; typically, nonionic surfactants are preferred because of biocompatibility, safety, less affected by pH and changes in ionic strength. In contrast, ionic surfactants are less preferred due to toxicological concerns [92]. Furthermore, solubilization of oil with the surfactant is also an important factor for surfactant selection, like Abdelaziz et al. selected Tween 20 and propylene glycol as surfactant and co-surfactant respectively on the basis of solubility of Indomethacin [93].

Likewise, Azeem et al., [72] and Arora et al. [54] identified Tween 20 and Tween 80 as the surfactant having highest solubility for oil phase Capryol 90 and oleic acid, respectively. However Pund et al., screened Tween 20, Tween 80, Labrasol, Cremophor RH 40 and Cremophor EL as surfactant where Capryol 90 used as oil phase [33]. Finally, they selected the surfactant on the basis of miscibility with oil phase along with solubility of drug (Leflunomide) in surfactant (Cremophor EL). Similarly, Shakeel et al. [94], elected Tween 80 as surfactant and Transcutol P as co-surfactant based on solubility of aceclofenac for phase study.

Natural surfactants generally from animal source, microbial cells like bacteria, few yeast and fungi are gaining research interest day by day due to their less toxic in nature, biocompatibility, environ compatibility and biodegradability. Biosurfactant are amphipophilic
in nature and they also reduce the interfacial tension by the same mechanism. Their polar head groups and short fatty acid tail has affinity to both hydrophilic and hydrophobic [49,95,96]. Bai and McClements used rhamnolipids as biosurfactant in formulation of nanoemulsion and they reported that rhamnolipids are effective natural surfactants which may be explored to replace synthetic surfactants in certain commercial applications [97,98]. On the other hand, Rosa et al. developed an stable o/w emulsion of d-tocotrienol-rich oil using saponin-rich extract from Brazilian ginseng roots as a biosurfactant [99]. Similarly, Cerón-Camacho et al. synthesized alkyl-O-glucoside and -cellobioside biosurfactants with a long fatty chain (C8–C18) in order to prepare stable and low viscous o/w emulsions of a Mexican heavy crude oil [100].

2.2.2. Co-surfactant

Co-surfactant helps surfactant in the nanoemulsion system to emulsify oil in aqueous phase. In such system, co-surfactant combines with surfactant and penetrates into the surfactant layer, thereby disrupts the interfacial film, and confers required fluidity, lower the interfacial tension, and help emulsification process [72]. Usually transient negative interfacial tension and fluid interfacial film cannot be achieved by using surfactant only, so incorporation of co-surfactant provide flexibility to the interfacial film. Co-surfactants may also help in solubilization of the oil by modification of the curvature of the oil-water interface [101]. Selection of co-surfactant is important because release of therapeutic agent or lipophilic drugs affected by its partitioning in aqueous and oil phase by interaction between surfactant and co surfactant [33]. Transcutol® HP, 1,2-propylene glycol, PEG-400,carbitol, absolute ethyl alcohol, propanol, butanol are used frequently as co-surfactants in nanoemulgel and nanoemulsion system [54,102]. Alcohols may increase the miscibility of the aqueous and oily phases due to its partitioning between these phases. Therefore, ethanol, isopropyl alcohol, 1-butanol, and propylene glycol are being selected as co-surfactants. PEG 400 and carbitol were also selected, as they show increased permeation when incorporated into formulations and are relatively tolerable [72]. The criterion of selecting surfactant and co-surfactant in nanoemulsion formulation is of their percent transmittance [103]. Arora et al. screened Tween 80, Labrasol, Labrafac as surfactant and Transcutol P, propylene glycol, ethanol as co surfactant using oleic acid as oil phase. In their formulations, Tween 80 revealed 96.34 ± 0.24% transmittance whereas the other surfactants labrasol and labrafac showed 89.41±0.66% and 72.66±0.69%, respectively [54]. Likewise, Transcutol P resulted in
higher percent transmittance than propylene glycol and ethanol and therefore, selected for the formulation development. Furthermore, Transcutol P was found to be advantageous as an efficient permeation enhancer [104]. Thus, it has been established that the concentration of co-surfactant influence the performance of surfactant in emulsification process. An assessment criterion for selection of co-surfactant is to evaluate the nanoemulsion area in phase diagram. Nanoemulsification efficiency of surfactant and co-surfactant ratio depends largely on the size of the nanoemulsion area in phase diagram. It had been reported that increased in carbon chain length on structure increased the nanoemulsion area [72].

On the other hand, mass ratio of surfactant and co-surfactant had also been found to be another key factor influencing the phase diagram properties, i.e., size and position of nanoemulsion region [105]. Abdelaziz et al. [93] and Azeem et al. [72] studied with Tween 20 and propylene glycol/carbitol as surfactant and co-surfactant respectively, reported that if co-surfactant is absent (1:0) or present at lower concentrations, the surfactant is not able to sufficiently reduce the interfacial tension. However, equal amount of surfactant and co-surfactant (1:1) leads to higher nanoemulsion region due to reduction in interfacial tension. On further increment of surfactant amount (2:1) increased the nanoemulsion area initially, followed by decrease in nanoemulsion area (3:1). This indicated that maximum emulsification reached at 2:1 ratio. Above findings were in coherence with Attwood et al. who also reported that location of nanoemulsion area in phase diagram changed with changing the ratio of surfactant (polysorbate 40) and co-surfactant (sorbitol) from 1:1 to 1:3.5. In the same way, Shakeel et al. found an increment of surfactant ratio upto 2:1 nanoemulsion area increased but further increase in surfactant concentration (3:1) leads to decrease in nanoemulsion area [94]. In contrast, Arora et al. [54] revealed that surfactant (Tween 80) alone showed significant nanoemulsion area in psuedoternary phase diagram, however, higher concentration of surfactant has also been reported to cause skin irritation [106]. So, it has been justified that incorporation of co-surfactant with surfactant leads to large nanoemulsification area due to good penetration of the oil phase in the hydrophobic region of the surfactant monomers. On the other hand, Bali et al. [92] grouped two formulations with Capryol 90 as oil phase with surfactant and co-surfactant of low (Labrasol and Transcutol® P) and high HLB (Tween 20 and PEG 400). They observed that an appreciable nanoemulsion region was obtained when high HLB surfactant (Tween 20) was used alone where incorporation of co-surfactant in equal quantity (1:1) nanoemulsion region was somewhat reduced. Conversely, in second group where surfactant and co-surfactant were
of low HLB values, small amount of oil was emulsified using high quantity of surfactant while addition of co-surfactant in equal quantity tremendously increase the nanoemulsion area [92].

Further, it has been reported that co-surfactant concentration is inversely proportional to the nanoemulsion region in phase diagram. Shafiq et al. [107] who investigated the nanoemulsion area in phase diagram was found to be decreased on increasing the co-surfactant concentration ratio in the mixture of Tween 80 (surfactant) and carbital (co-surfactant). Similarly, [93] also observed that the increase in concentration of co-surfactant with respect to surfactant (1:2) could result in decreased nanoemulsion area compared to 1:1 ratio. It was reported that two non-ionic surfactants with different HLB values able to produced more stable emulsion in comparison to mixture of surfactant and co-surfactant of having close HLB values. This may be attributable to the fact that surfactants with higher HLB values solubilize in the aqueous phase, whereas lower HLB values solubilize in oil that enable to work more strongly with surfactant and co-surfactant mixture [85,108]. Based on same concept, Shakeel et al. [94], selected Tween 80 having HLB value of 15 along with Transcutol P, which has an HLB value of 4.2 to produce stable nanoemulsion.

Thus, it has been observed that selection of ideal components for a nanoemulsion is a challenging part of research. In the connecting section of the article, we will discuss on the different formulation procedure aspects to formulate nanoemulsion in the laboratory and the use of diverse hydrogels to change the physical status of the formulated nanoemulsion.

3. Preparation of nanoemulsion and change its physical state by addition of gelling agent:

Nanoemulgels are manufactured undergoing two steps, where in the first step nanoemulsion will be manufactured whereas nanoemulsion will be introduced in the gelling agent during the second step (Figure 3). Nanoemulsions are spontaneously prepared by mixing the compositions by reducing the interfacial tension between oil/water interfaces or may be prepared by application of external energy into the heterogenous mixture [109,110]. Thus, a thermodynamically stable nanoemulsion can be prepared basically by adopting high energy and low-energy emulsification methods.

Step 1:

*High-Energy Emulsification Method*
High shear force produced by ultrasonicators, high pressure homogenisers, microfluidizers, etc., are used to rupture the oil phase to form nanosized droplets in the aqueous phase by optimizing required time, temperature and component properties to minimize size of the dispersed to the nano-range [98,111,112]. Therefore, this methods of preparation of nanoemulsion require input of external energy which makes the developed formulations thermodynamically unstable due to the presence of free energy into it [73,113]. Further, this method is advantageous to obtain the size of the dispersed phase as low as 1 nm through component changing, whereas it is inapplicable for thermolabile components [19].

**Low Energy Emulsification Method**

Low-energy method for preparation of nanoemulsions include spontaneous method and phase inversion method, which are found to be advantageous over high energy emulsification technique in terms of thermodynamic stability of the final formulation due to incorporation of high energy during manufacturing process [10,19]. Mixing of oil, water and surfactant in a perfect ratio could formulate the nanoemulsion spontaneously, alternatively by addition of aqueous phase with or without surfactant in the oil phase without or with surfactant, respectively could generate desired nano-structured droplets dispersed in the continuous phase. The order of addition of the basic components, pH of the medium, properties of incorporated surfactant and co-surfactant affect the emulsification process [19]. Specifically, temperature dependent change in HLB for certain non-ionic surfactants, mostly polyethoxylated surfactants (e.g., Tween 80, Tween 60, Tween 20, Cremophor EL, Labrasol, etc.) are utilized under this method [114,115]. Spontaneous method is most suitable for the thermolabile components to be incorporated into the nanoemulsion. Alternatively, temperature dependent spontaneous twist of non-ionic surfactants is used for phase transition during phase inversion method. The emulsion formed at phase inversion temperature will be reversed on cooling with continuous stirring. This process is also limited to incorporate thermolabile components, although this limitation could be reverted by approaching decreased phase inversion temperature by suitably selecting the surfactant(s) [19,116].
Step 2:

Nanoemulsion prepared by adopting any of the above methods can be converted to nanoemulgel using gelling agents. Purpose of use of jelling agent in the nanoemulsion formulation is to change its physical state, from liquid to gel. Addition of gelling agent to an o/w nanoemulsion system thickens the formulation by forming gelled like structure. This is due to the thixotropic nature of the agent which helps in the gel-solution transition during application of shear stress to the formulation without changing its volume. Further, on standing, there will be an automatic reversal of the state from solution to gel. Some commonly used gelling agents are used in the preparation of nanoemulsion gel, which includes carbomer 940 [54], chitosan [117], carbopol 934 [39,42,118], carbopol 940 [32,40,119], carbopol-980 [120], Poloxamer 407 [42], methyl cellulose [121], carbopol 971 [58] etc. Incorporation of gelling agent in the nanoemulsion had been shown to affect the pharmacokinetic properties of the drug incorporated into this nanocarrier system. Gelling media is prepared by dissolving gelling agents into an aqueous media with continuous stirring at a constant rate at specified conditions for specific time to obtain complete swelling. Finally, the emulsion will be introduced into the prepared gel at a particular ratio with continuous mixing for homogeneity [59]. Impact of nanoemulgel development in the pharmacokinetic and pharmacodynamic properties of the drug has been summarized in the following section of the article.

4. Brief testimony of published nanoemulgel formulations and its impact on pharmacology

Incorporation of hydrogel matrix in nanoemulsion could have a high impact on the pharmacokinetic properties of the drug. Lipophilic drugs are mostly incorporated into the lipid phase before preparation of the nanoemulsion. Screening of lipid phase for perfect choice for the incorporated drug as well as estimation of entrapment of the pharmaceutical component into the nanoemulsion specially determines using modern analytical instruments, like HPLC [9,122]. In a recent study by Dasgupta et al. reported the development and optimization of lornoxicam nanoemulgel [76]. However, instead of directly adding optimized nanoemulsion to gelling agent, as described earlier (1% w/w Carbopol 934), here the researchers adopted a different strategy. They added the selected oil, Labrafac, first to the dispersed phase of gelling agent followed by addition of triethanolamine to neutralize the gel. Selected surfactant (Tween 80) and co-surfactant (Pluronic F68) were slowly integrated into the gel and thus nanoemulgel was formed by adding rest of the aqueous phase. The pH of
developed nanoemulgel was found to be 6–7 following neutralization using 0.5% w/w triethanolamine, and it has also reported that the neutral pH is appropriate for cutaneous application [55]. In vitro release and permeation flux through skin are significantly higher for nanoemulsion and nanoemulgel compared to marketed gel formulation whereas in vitro release and permeation flux of lornoxicam was found to be maximum in nanoemulsion formulation. Less flux of nanoemulgel compared to nanoemulsion may result in prolonged drug release behavior of nanoemulgel. Hence pharmacodynamic study revealed that both nanoemulsion and nanoemulgel remained superior to the marketed product in its ability to suppress edema in Complete Freund’s Adjuvent induced paw edema model in male Wistar rats [76]. In another study by Khurana and team revealed the sustained release and enhanced permeation properties of the meloxicam carrier gel through skin, simultaneously, the developed formulation was found to be non-irritant, hemo-compatible, and non-toxic with significant anti-inflammatory activity [119].

Study by Pund et al. disclosed nanoemulgel as potential carrier for the treatment of psoriatic arthritis and melanoma affected skin. The research team had successfully improved ex-vivo permeability of the drug through rat skin, to mimic the transdermal permeability of the formulation. Further, developed formulation was found to cause cell specific cytotoxicity towards human melanoma cell lines, which further proves the safety of the formulation towards normal cells. They had postulated that this transdermal delivery could be targeted to site specific treatment thereby it will reduce the dose of the drug, leading to be economically helpful as well as minimize systemic adverse events [33]. Histopathological sections of the rat skin showed no alteration of the skin architecture following 12 hour of exposure with nanoemulsion (Figure 4c), whereas positive control group with nitric oxide (Figure 4b) showed marked alteration of the epithelium as compared to negative control (Figure 4a). In vitro study on A375 and SK-MEL-2 cell line demonstrate the upregulation of the aryl hydrocarbon receptors and antiproliferative activity in the test cell lines through activation of the transcriptional activity [33]. Similar approach towards mycological cure with nystatin nanoemulgel resulted in highest drug release when compared with solid dispersion or marketed cream formulation [121]. Carbopol 934 was employed by Aparna and team during preparation of nanoemulsion of telmisartan, an antihypertensive agent. In their study, the ex-vivo skin permeation results were found to be correlated with the in vivo findings. Both the studies showed significant increase in the drug permeability. This could be possible due the enormous increase in the surface area of the drug in the nanoemulsion which further enhances its solubility as well as its permeation through the lipidic tissue barriers [39].
Another study by Elosaily et al. reported the prepared nanoemulsion of nystatin by spontaneous emulsification technique and further modified to nanoemulgel by adding to viscous solution of 5% methyl cellulose. The group compared the formulated nanoemulgel to solid dispersion gel of the drug and observed that the release of nanoemulgel is higher compared to solid dispersion gel. Besides, it is relevant to mention that the nanoemulgel of nystatin also showed increased efficacy and better tolerability against cutaneous candidiasis in clinical trial compared to the Nystatin® cream [123].

In another study, itraconazole nanoemulgel was developed by Sampathi et al. where they developed the nanoemulsion by ultrasonication after dissolving the drug in eugenol by heating with lecithine and sodium cholate as surfactants. Optimized nanoemulsion was converted to nanoemulgel by using carbopol 934 and the pH was adjusted by triethylamine [124]. Here, the researchers used 0.1% limonene in the formulation as permeation enhancer as well as odor masking agent. Nanoemulsion based hydrogel of itraconazole showed promising penetration and in vitro release when compared to the drug solution. Interestingly, the formulation showed sustained release profile which might be helpful in reduction of the dosing frequency [124]. In a similar type of study, Mirza et al. also developed nanoemulgel formulation of itraconazole with tea tree oil using Tween 20, labrasol, and carbopol 934 as surfactant, co-surfactant and gelling agent, respectively. Findings of their study revealed that in spite of similar polymer content, a higher flux and improved permeability of the drug can be achieved with nanoemulgel formulation than the conventional gel. Additionally, preparation of nanoemulgel of itraconazole in tea tree oil (as proposed to have antimicrobial activity) potentiates the antimicrobial property of the drug due to synergistic effect [42].

Eid and team had developed a nanoemulsion formulation of Swietenia macrophylla oil, using an oil phase to observe its therapeutic efficacy by phase inversion method followed by self-emulsification. Optimized nanoemulsion was further modified to gel by using carbopol 940 as gelling agent. Swietenia macrophylla oil nanoemulgel was shown to have significant anti-inflammatory activity in carrageenan induced rat paw edema compared to Swietenia macrophylla oil solution [71]. A brief summary of transdermal nanoemulgels for its components, droplet size of the dispersed phase and overview of reported pharmacological properties have been summarized in Table 1.

Full epidermis layer of our skin provides a protective barrier for any hazardous substance to enter into the body. Thus, penetration of hydrophilic drugs and high molecular
weight compounds having size >500 Da are limited through intact skin [125]. Being larger in size and peculiar problems associated with oral delivery, viz: poor aqueous solubility, poor permeability and acidic degradation [126], amphotericin B is available as parenteral dosage form. To overcome the limitations of clinical application including potential nephrotoxicity of amphotericin B, an approach in formulation development has been accomplished by Hussain and team [127]. Topical route has been chosen for the new formulations to acquire antifungal activity as well as to avoid serious systemic complications of the drug. The researchers developed the nanoemulgel of amphotericin B by incorporating formulated nanoemulsion to the dispersed polymeric gelling agent (carbopol-980) followed by vigorous homogenization. In the optimization of nanoemulsion selfsol 218 and dimethyl sulfoxide in 1:1 ratio has been selected as appropriate oil phase. Triethylamine was added to the dispersed gelling agent and kept overnight for air removal and for cross linking the polymer with triethylamine. Experimental in vitro results on release, skin permeation and hemolysis studies were satisfactory and further skin irritation test in Wistar albino rats did not result in erythema or edema as observed at different time points after application of the formulation. Additionally, to clarify in vitro permeability outcomes, in vivo study for skin penetration was performed by incorporating Rhodamine 123 (a tracer dye) in nanoemulgel and nanoemulsion to observe the penetration of drug through skin by using Fluorescence Correlation Microscope [127]. Low viscosity of nanoemulgel and nanoemulsion of amphotericin B resulted in slow release/sustained release in initial hours compared to the solution. Further, sustained release pattern of nanoformulation follow zero order kinetics whereas release of drug from solution follows first order kinetics. Interestingly cumulative drug permeation of nanoemulgel is higher compared to nanoemulsion and conventional gel. It will be very commendable that combination of transcutol-P and tween 80 have synergistic effect on improvement of drug permeation through skin, even to the high molecular weight drugs. Finally, pharmacodynamic efficacy of the formulation was established by in vitro antifungal activity, thus the safety pattern revealed its effectiveness over oral delivery of amphotericin B [127].

Arora and team had formulated a novel nanoemulsion with ketoprofen using low energy method where carbomer 940 was used to convert nanoemulsion to nanoemulgel. The group selected the excipients based on solubility studies, transmittance and further formulation was optimized based on thermodynamic stability, drug content, spreadability, rheological properties, ex vivo drug permeation study and sustainability studies at stress
conditions. Nanoemulgel was surprisingly found to significant higher permeation and flux with lower lag time than the marketed formulation and solution [54] which further inspire the researcher to work on nanoemulgel to ensure the commercialization of nanoemulgel. It is interesting to mention that the concentration of surfactant-co-surfactant is inversely proportional to the penetrability. In this experimentation, the researchers mentioned that upon reduction of surfactant-co-surfactant concentration from 75% to less than half (35%), the penetration rate was doubled. This statement was also supported by another team of researchers [106]. Researchers further commented that salvation of $\alpha$-keratin layer of the skin and formation of hydrogen bonding property of transcutol P could further help in penetration of the drug through the intact skin [54,104]. Study of stratifin and acetylsalicylic acid loaded nanoemulgel showed a sustained release profile of the drugs which dramatically improve the wound healing on rabbit ear with a daily basis dressing. With this decreased number of application of this formulation over the wound bed, it was found to reduce epidermal hypertrophy better than the CMC gel of the drugs and a significant reduction in both collagen density and tissue cellularity [45].

Low energy method was employed by Yang and group for the preparation of microemulgel of diclofenac sodium using chitosan and cationic polymer polylysine. On evaluating it was found that the skin permeation rate of the drug from the optimized formulation was 1.86- and 5.76- folds higher, respectively than that of the commercial emulgel and hydrogel formulation of the same drug. Interestingly, self-preserving activity of the reported micro-emulgel was an immense observation by the authors when used polylysine in the formulation [128].

Delivery of nanoemulgel is not only limited to the transdermal application, it has gained interest by the researchers towards application in periodontitis disease, ocular delivery, cosmetology, vaginal infection etc. Srivastava et al. [43] had developed nanoemulgel of a non-steroidal anti-inflammatory agent (NSAID), ketoprofen, for periodontics disease where they used eugenol as an oil and Carbopol 934P and Polaxamer 407 as gelling agents. They observed that high concentration of polaxamer 407 results in slower burst release of drug from nanoemulgel. On evaluation of the pharmacodynamic efficacy in periodontitis, it was observed that ketoprofen nanoemulgel significantly reduced gingival index, tooth mobility, alveolar bone loss [70]. Pharmacodynamic activity was reflected by the decreased levels of cytokine close to the normal in ketoprofen nanoemulgel
treated group. Additionally, significant reduction in inflammatory cell infiltration, alveolar bones resorption and cementum were evident from the histopathological analysis of the experimental molar teeth as observed with ketoprofen nanoemulgel treated group. Eugenol oil used in formulation development has shown synergistic effect to ketoprofen in the control of periodontitis [70].

For the remedial action on arthritic disorder, Jeenger et al. recently reported the development of Curcumin nanoemulsion formulated with emu oil. This delivery of Curcumin loaded nanoemulsion loaded in carbopol gel was found to solve the poor penetration and low solubility characteristics of curcumin. In the experimental model of adjuvant induced arthritis, it was observed that the destruction of bone was significantly reduced as evidenced by the decrease in radiological scoring through application of low and high dose curcumin nanoemulsion loaded gel (Figure 5). The findings were further proved through inhibition of cartilage damage, decrease in cellular infiltration in synovial cavity, prevention of damage and narrowing of synovial space, and pannus formation. Figure 6 represents the histopathological diagram on improvement of arthritic condition in the experimentally induced arthritic rats [59].

Nanoemulgel is also considered to be a promising alternative drug delivery to the conventional eye drops. Due to gel like droplet of nanoemulgel formulation, sufficient drug quantity can be incorporated and delivered to the cornea and the aqueous humor parts of the eye. Tayel and team had developed a controlled release ocular nanoemulgel of terbinafine, an allylamine antifungal compound, where the researchers used Miglyol 812 as oil phase and Cremophor EL, PEG 400 and gellan gum as surfactant, co-surfactant and gelling agent, respectively [44]. Aqueous solution of gellan gum was heated to 50°C and 0.5% drug loaded nanoemulgel was prepared by mixing optimized nanoemulsion formulation to the gellan gum solution. Special property of gellan gum attracted its use in ocular nanoemulgel delivery. Gellan gum cross links with the tear fluid electrolytes and proteins allowing in-situ gelation, as assessed by using simulated tear fluid, thereby provides a prolonged release. The optimized nanoemulgel was sterilized by using gamma radiation in presence of dry ice [44]. Pharmacokinetic findings in rabbit plasma revealed significantly higher $C_{\text{max}}$, delayed $T_{\text{max}}$, prolonged mean residence time and increased bioavailability profile of the drug. Interestingly, the ocular irritation potential of the drug in nanoemulgel was found to be very less [44,79]. Pathak and his coworkers also developed an ocular nanoemulgel formulation of
fluconazole, a triazole antifungal agent, using capmul MCM as oil phase, emulsified with tween 80 and transcutol P and gelled with carbopol 934. The in vitro antifungal activity of the nanoemulgel formulation showed to have higher antifungal activity as compared to the fluconazole solution. Additionally, a 3.71 folds higher cumulative amount of fluconazole permeation was observed from nanoemulgel formulation compared to commercial eye drop preparation [69]. A higher rate of cumulative drug permeation has also been reported from diclofenac diethylamine nanoemulgel formulation when formulated with oleic acid as oil base, Polysorbate 20 and ethanol as surfactants and carbopol 971 as gelling agent [129].

Incorporation of nanotechnology is common in cosmetology. Harwansh et al. developed a nanoemulgel with ferulic acid, a strong UV absorber that prevents UV induced skin damage, by dispersing the pre-soaked gelling agent (carbopol 940) in distilled water into the optimized nanoemulsion which was developed by adopting low pressure method [40]. In order to obtain a homogeneous dispersion of gel, the researchers incorporated components like polyethylene glycol 400, propylene glycol, isopropyl alcohol and triethanolamine into the nanoemulgel. In vitro permeability of the formulated nanoemulgel was found to be directly comparable to the droplet size in the formulations. Further, the improved permeability and controlled release property was found to be effective against UV exposure even after 4 h of application to the skin surface [40]. Introduction of nanotechnology through adaptation of nanoemulgel approach for vaginal, dental, ocular and transangual application has been summarized in Table 2.

5. Concluding remark and future prospect:

Nanoemulgel contains various constituents and the nature of selection along with determination of desired concentration of such components requires a skilled knowledge because the properties of these are varying from components to components, whether it is surfactant, co-surfactant, oil and/or gelling agent. Further, different manufacturing methodologies have distinct advantages which affect the characteristics of the final formulation. Thus, development of a thermodynamically stable nanoemulsion and nanoemulsion to nanoemulgel is solely depending on suitable selection of its components and the primary methodology. Formulating hydrogel thickened nanoemulgel from nanoemulsion has found to be better compatible and efficient than the ordinary nanoemulsions for transdermal delivery. This viscous formulation could be more thermodynamically stable than nanoemulsion due to reduction of interfacial tension and decreased mobility of the dispersed
phase, thus could result in better and successful topical delivery system of pharmaceutical agents, particularly for lipophilic drug molecules with the aim of enhanced skin permeation across the deeper layer of the skin due to improved contact time, formation of thin layer over the skin and by hydrating the skin. Marketed formulations for this nanoemulgels are pointing towards potential improvement in therapeutic aspects and research interest of this novel dosage forms.

Successful incorporation of nanoemulsion in hydrogel with improved therapeutic response in various pathophysiological condition suggesting a significant progress of formulation scientists in pharmaceutical industry. Nevertheless, it creates a center of attention for user acceptability due to the non-greasy-gel like sustained release property following topical administration. Incorporation of active components against bacterial, fungal, viral infections or even for melanoma can be extrapolated successfully through development of nanoemulgel, however more molecular assessment on absorption process of the drugs should be necessary. Therefore, this novel transdermal dosage form is open for research to target specific dermatological disorders as well as in the improvement of various systemic ailments.

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Figure captions:

Figure 1: Possible strategies to improve bioavailability of poorly water soluble drugs.

Figure 2: Strategies for oil phase selection in the course of nanoemulgel formulation development.

Figure 3: Schematic representation of nanoemulgel preparation: Step 1 - Preparation of nanoemulsion; Step 2 - Conversion of nanoemulsion to nanoemulgel.

Figure 4: Histopathological sections of rat abdominal skin (magnification 40x) (a) negative control, untreated skin, (b) positive control, skin treated with nitric acid (37% v/v) for 2 h, and (c) test specimen, skin treated with leflunomide nanoemulgel for 12 h. [33].

Figure 5: (A) Radiological scoring of adjuvant arthritic and treated rats. All the values are expressed as mean ±SEM (n = 6). ***P < 0.001 and *p < 0.05 vs. Adjuvant induced arthritis (AIA); control; %p < 0.001, %p < 0.01 vs. standard (STD; indomethacin) group; ##p < 0.001, ##p < 0.01 vs. BF. (B) Radiographic changes in ankle joints; normal, no evidence of pathological changes was observed in normal animals, AIA control group showing severe inflammation with diffused joint space, cartilage destruction and bone deformity along with bone erosion; STD, Clear joint space and no evidence of inflammation and bone loss in standard diclofenac treated group; BF, blank nano emulsion loaded gel treated group also showed severe inflammation and bone loss moderate deformity; CFL, curcumin nanoemulsion loaded gel (low dose) and CFH, curcumin nano emulsion loaded gel (high dose) both groups showed recovery and was similar to standard group. S, soft tissue swelling; D, deformity; E, erosion [59].

Figure 6: Effect of treatment of diclofenac gel and curcumin nano emulsion loaded gel on tibiotalcal joint histology in different groups of rats. Sections were cut sagittally, stained with hematoxylin/eosin and photographed at magnification of 100x. Ti, tibia; Ta, talus; SS, synovial space; C, cartilage; ST, synovial tissue; CI, cellular infiltrate [59].
Table captions:

Table 1: Summary of reported transdermal nanoemulgels for its components, formulation droplet size and overview of reported pharmacological properties with rationalisation in the findings.
Table 2: Summary of reported vaginal, dental, ocular and transangual nanoemulgels for its components, formulation droplet size and overview of reported pharmacological properties with rationalisation in the findings.
Table 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oil</th>
<th>Surfactant Co surfactant</th>
<th>Gelling agent</th>
<th>Droplet size</th>
<th>Safety</th>
<th>Efficacy</th>
<th>Skin permeation</th>
<th>Remarks</th>
<th>Ref.</th>
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</thead>
<tbody>
<tr>
<td>Curcumin</td>
<td>Emu oil</td>
<td>Cremophor RH40 and Labrafil M2125CS oil:surfactant:cosurfatant:: 2:5:3</td>
<td>Carbopol gel</td>
<td>62.06 ± 0.52 nm</td>
<td>-</td>
<td>significant improvement in antiinflammatory activity</td>
<td></td>
<td>Increased permeation, anti-inflammatory, analgesic activity is due to nano droplet and presence of emu oil in nanoemulgell.</td>
<td>[59]</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Oleic acid (6% w/w)</td>
<td>Tween 80 Transcutol P (35% w/w)</td>
<td>Carbomer 940</td>
<td>55.40 ± 0.58 nm</td>
<td>-</td>
<td>-</td>
<td>The nanoemulgell had higher flux, high permeation potential, lower local accumulation efficiency compared to solution and marketed formulation.</td>
<td>Oleic acid, Transcutol P was reported as permeation enhancer. (Note: with very high concentration of oleic acid: permeation decrease due to aggregation of oil)</td>
<td>[54]</td>
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<tr>
<td>Capsaicin</td>
<td>Glycerol monooleate</td>
<td>Poloxamer 407 and Glycerol</td>
<td>Carbopol 940</td>
<td>170.30± 7.81 nm</td>
<td>Produce no observable skin irritation in rabbits within 72h.</td>
<td>Not reported</td>
<td>Capsaicin Permeability in nanoemulgell was 2.80-fold greater flux values than conventional ointment after 24 h.</td>
<td>Shear rate had a positive correlation with entrapment efficiency and a negative correlation with particle size and polydispersity index.</td>
<td>[130]</td>
</tr>
<tr>
<td>Ferulic acid</td>
<td>Isostearyl isostearate</td>
<td>Labrasol, and plurol isostearique</td>
<td>Carbopol 940</td>
<td>105 ± 0.14 nm</td>
<td>The nano-gel was found to be stable, safe and effective for topical application against UV.</td>
<td>Sustained release effect against UV A exposure with enhanced UV protection activity.</td>
<td>The nanogel formulation exhibited better permeation profile (96.95%) in comparison with conventional gel (61%) at 24h.</td>
<td>Drug loaded nanogel exhibited better UV protection activity even after 4 h of application to the skin surface due to its improved permeability and sustained-release profile.</td>
<td>[40]</td>
</tr>
<tr>
<td>Lornoxicam</td>
<td>Labrafac</td>
<td>Tween 80 and Pluronic F68</td>
<td>Carbopol 934</td>
<td>102 to 200 nm</td>
<td>-</td>
<td>The formulation found to be superior to the marketed product</td>
<td>The steady-state flux and permeability coefficient were significantly</td>
<td>Composition like tween 80 and labrafac also act as a permeationenhancer through skin.</td>
<td>[76]</td>
</tr>
<tr>
<td>Drug</td>
<td>Oil</td>
<td>Surfactant Co surfactant</td>
<td>Gelling agent</td>
<td>Droplet size</td>
<td>Safety</td>
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<tr>
<td>Amphotericin B</td>
<td>Sefsol-218</td>
<td>Tween 80 and Transcutol-P</td>
<td>Carbopol-980</td>
<td>76.2±1.4 nm</td>
<td>No severe irritation symptoms such as erythema and edema observed to the rat skin.</td>
<td><em>In vivo</em> histopathological examination suggested that the formulation is more efficacious than oral delivery for cutaneous infection. The flux rate of nonoemulgel found to be 3.9-3.5 fold higher with respect to the solution.</td>
<td>Significant enhancement of the permeation was achieved by the use of 5% DMSO.</td>
<td>[127]</td>
<td></td>
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<tr>
<td>Meloxicam</td>
<td>Cetyl palmitate</td>
<td>Tween 80 and Propylene glycol</td>
<td>Carbopol 940</td>
<td>239.33 ± 0.88 nm</td>
<td>Solid lipid nanoparticle gel did not result in any marked changes in normal histology and no inflammation in skin</td>
<td>Effectively suppressed carrageenan induced paw edema and sustained activity was observed with solid lipid nanoparticle gel Meloxicam deposited in varying amount at different layer of the skin. Epidermis&gt; Dermis&gt; Subcutaneous layer</td>
<td>-</td>
<td>[32]</td>
<td></td>
</tr>
<tr>
<td>Nystatin</td>
<td>Labrafilm M</td>
<td>Tween 80 and ethanol</td>
<td>Methyl cellulose</td>
<td>Clinical trial showed the nanoemulgel was more efficacious and better tolerated than commercially available cream for the treatment of cutaneous candidiasis.</td>
<td>Showed to have significantly higher rates of mycological cure.</td>
<td>-</td>
<td>In a clinical trial study, nanoemulgel of nystatin has been proved a promising drug delivery against cutaneous candidiasis.</td>
<td>[123]</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Eugenol</td>
<td>Lecithine and Carbopol</td>
<td>154.3 to Non-irritant to -</td>
<td>Compared to solution,</td>
<td>-</td>
<td></td>
<td>[124]</td>
<td></td>
<td></td>
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<tr>
<td>Drug</td>
<td>Oil</td>
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<tr>
<td>Leflunomide</td>
<td>Capryol 90 and Transcutol HP</td>
<td>Cremophor EL and Transcutol HP</td>
<td>Pluronic F127</td>
<td>98.7–280.92 nm</td>
<td>No hemolytic and local tissue toxicity was observed.</td>
<td>Cytotoxicity studies showed enhanced therapeutic response against psoriasis and melanoma.</td>
<td>Ex vivo studies demonstrated that nanoemulsification significantly promoted the transcutaneous penetration and skin deposition of the drug.</td>
<td>Leflunomide nanoemulgel showed effective localization which may result in dose reduction and reduction in systemic toxicity.</td>
<td>[33]</td>
</tr>
<tr>
<td>Swietenia macrophylla oil</td>
<td>Swietenia macrophylla oil (50%), sucrose laurate (20%), glycerol (30%)</td>
<td>Carbopol 940</td>
<td>113 to 117 nm</td>
<td>-</td>
<td>Significant anti-inflammatory activity was observed in nanoemulgel treated group in carrageenan induced paw edema model.</td>
<td>The group proved that carbopol 940 is superior than carbopol 934 as a viscosity modifier for nanoemulgel formulation.</td>
<td>[71]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diclofenac diethylamine</td>
<td>Oleic acid and ethanol</td>
<td>Polysorbate 20 and ethanol</td>
<td>Carbopol 971P</td>
<td>59.97±3.22 nm</td>
<td>-</td>
<td>-</td>
<td>The cumulative amount of drug permeation was higher in nanoemulgel.</td>
<td>[129]</td>
<td></td>
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</table>
Table 2

<table>
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<tr>
<th>Drug</th>
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<th>Surfactant</th>
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<th>Ref.</th>
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<tbody>
<tr>
<td>Vaginal nanoemulgel</td>
<td></td>
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<tr>
<td>Itraconazole</td>
<td>Tea tree oil</td>
<td>Tween 20 and Labrasol</td>
<td>Carbopol 934</td>
<td>Average diameter 42.13 nm</td>
<td>The optimized gel was also found without any sign of toxicity.</td>
<td>The dual loading of Itraconazole and tea tree oil in a single formulation showed to be more effective as antimicrobials.</td>
<td>In spite of similar polymer content, a higher flux was obtained with nanoemulgel formulation than the conventional gel.</td>
<td>Despite being low solubility of Itraconazole in tea tree oil, a homogenous, transparent and stable solution of both was created by co-solvency using chloroform.</td>
<td>[42]</td>
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Dental nanoemulgel

<table>
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<th>Gelling agent</th>
<th>Droplet size</th>
<th>Safety</th>
<th>Efficacy</th>
<th>Skin permeation</th>
<th>Remarks</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoprofen</td>
<td>Eugenol (13%)</td>
<td>Cremophore EL and Transcutol HP (37%)</td>
<td>Carbopol 934P and Polaxamer 407</td>
<td>37.230 ± 0.210 nm</td>
<td>Not irritant to mucous membrane (evaluated invivo using HET-CAM method); Suitable for intrapocket delivery.</td>
<td>Suitable formulation for periodontal disease in respect of syringibility, mucoadhesivity and rheology. Nanoemulgel significantly prevent periodontitis by preventing like gingival index, tooth mobility, alveolar bone loss.</td>
<td>Box–Behnken experimental design (3-factor 3-level) was used for the optimization of nanoemulsion. Due to antibacterial, analgesic and anesthetic properties of eugenol, synergistic potential of ketoprofen and eugenol was observed in periodontitis</td>
<td>[43, 70]</td>
<td></td>
</tr>
</tbody>
</table>

Ocular nanoemulgel

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oil</th>
<th>Surfactant</th>
<th>Gelling agent</th>
<th>Droplet size</th>
<th>Safety</th>
<th>Efficacy</th>
<th>Skin permeation</th>
<th>Remarks</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terbinafine hydrochloride</td>
<td>Miglyol 812</td>
<td>Cremophor EL and PEG 400</td>
<td>Gellan gum</td>
<td>Less than 30 nm</td>
<td>Showed no histopathological alteration in the cornea, iris, retina or sclera in rabbit.</td>
<td></td>
<td></td>
<td>Nonoeulgel showed the least ocular irritation potential and significantly higher C_{max}, delayed T_{max}, prolonged mean residence time and increased</td>
<td>[44]</td>
</tr>
<tr>
<td>Drug</td>
<td>Oil</td>
<td>Surfactant Co surfactant</td>
<td>Gelling agent</td>
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<tr>
<td>Fluconazole</td>
<td>Capmul MCM</td>
<td>Tween 80 and Transcutol P</td>
<td>Carbopol 934</td>
<td>19.09 ± 1.93 nm</td>
<td>Ex-vivo corneal toxicity study demonstrated ocular safety of the formulation.</td>
<td><em>In-vitro</em> antifungal activity showed to have better antifungal activity of the nanoemulgel compared to the solution.</td>
<td>A 3.71 folds higher cumulative amount of fluconazole permeation was observed from nanoemulgel compared to commercial eye drop.</td>
<td>The droplet size decreased with increasing surfactant to cosurfactant ratio.</td>
<td>[69]</td>
</tr>
<tr>
<td>Transangual</td>
<td>Labrafac™ Lipophile WL1349</td>
<td>Tween 80 and PEG 400</td>
<td>Carbopol® Ultrez 21</td>
<td>77.52 ± 0.92 nm</td>
<td>After 48 hour of incubation showed a significant area of zone of inhibition for T. rubrum and C. albicans) due to slow diffusion of nano droplet into the medium although during first 24 hour nanoemulgel exhibited similar activity like drug solution</td>
<td>Exvivo trasungual permeation study was carried out using goat hoof membrane. Improved permeation for nanomulsion and nanoemulgel was observed in compare to aqueous suspension of ketoconazole.</td>
<td>Nanoemulgel could be a better choice for the treatment of onychomycosis</td>
<td>[77]</td>
<td></td>
</tr>
</tbody>
</table>
Strategies to improve solubility and bioavailability of lipophilic drugs

- Crystal Engineering
  - Co-crystal formation
  - Salt formation
  - Polymorphs

- Lipid based systems (LBS)
  - Nano sized LBS
  - Self emulsifying LBS
  - Micro-emulsion
  - Liposomes and pro-liposomes

- Solid Lipid Nanoparticles

- Nano-structured lipid particles

- Meso-porous Silica Nanoparticles systems
  - Polymeric systems
  - Polymeric micelle
  - Polymeric nanoparticles
  - Dendrimers

- Carbon nanoparticles (Nanotube) systems
Oil selection for Nanoemulgel

Oil from natural sources: medicinal values
- Chicory acid:
  - Orange oily fluid
  - Biocompatible, biodegradable
  - Excellent absorbency, penetrating
  - Antioxidant, anti-inflammatory

- Tea tree oil:
  - Broad spectrum antimicrobial activity
  - Audiolistic selection of concentration
  - Anti-inflammatory, anti-bacterial, anti-fungal, anti-viral

- Emu oil:
  - Anti-inflammatory analgesic
  - Anesthetic anti-irritant, anti-inflammatory

- Eucalyptus:
  - Anti-inflammatory, analgesic,
  - Anti-irritant, anti-bacterial

Edible oil: Not frequently used
- Lemon oil:
  - Not frequently used

Chemically modified oil: Medium chain mono, di or tri glyceride
- Capryol 90:
  - Miglyol 812 - well tolerated to human eye
- Labrafac:
  - Caprol MCM - well tolerated to human eye