European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 10, Issue 01, 2023

Future Aspects And Applications Of Nanoemulgel Formulation For Topical Lipophilic Drug Delivery

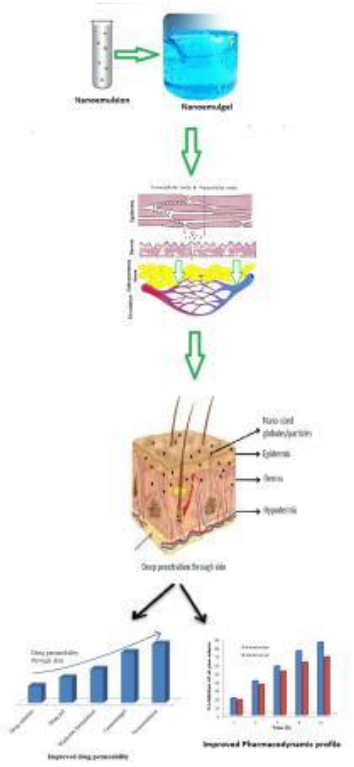
Suraj Mandal[1*], Dr. Prabhakar Vishvakarma[2]

[1] Research Scholar, IIMT College of Medical Sciences, IIMT University, O-Pocket, Ganga Nagar, Meerut, U.P., 250001, India.

[2] Associate Professor, IIMT College of Medical Sciences, IIMT University, O-Pocket, Ganga Nagar, Meerut, U.P., 250001, India.

Corresponding Author Details-
Suraj Mandal,
Research Scholar, IIMT College of Medical Science, IIMT University, O-Pocket, Ganga Nagar, Meerut, U.P., India, 250001
Email: sk8006721807@gmail.com
ORCID I'd: 0000-0001-5080-7855

Graphical Abstract:



ABSTRACT:

Most recently developed medicines have restricted absorption and pharmacokinetic variability as a result of their lipophilic nature. The objective of this study is to assess and discuss nanoemulgel formulation as a useful delivery technique for medicines that are poorly soluble in water. One of two techniques can be used to incorporate a drug-containing nanoemulsion

into a nanoemulgel's gel foundation. This formulation has a lot of benefits as a result of the combination of these two systems. Lipophilic drugs can be easily absorbed and their skin permeability enhanced by the finely dispersed oil droplets that are present in the gel phase. Additionally, it can more precisely target the online action, lessen the user's gastric and systemic intolerances, and save you time by skipping metabolism. This device is a formulation-related intervention that enhances lipophilic drug treatments' absorption and healing profile. Because of their improved patient acceptability, non-greasy, pleasant spreadability, uncomplicated administration, and high therapeutic and safety profile, the use of nanoemulgels has lately increased. Despite their minor disadvantages, nanoemulgel compositions may one day be significant rivals for the topical administration of lipophilic medications.

Keywords: Nanoemulgel, nanoemulsion, drug delivery, bioavailability, topical administration, spreadibility

1. Introduction:

An emulsion is a dispersion system consisting of finely dispersed droplets in a non-agitated vehicle. Macroemulsions (droplets with a diameter of 1 to 100 µm) are also referred to as conventional emulsion/colloid, emulsion types are classified according to the droplet. generally unstable in water droplets or nearly buoyant with one and a half parts dispersion, readily absorbed by solid particles on the surface. While microemulsions (droplets between 10-100nm) are an isotropic liquid system with more uniform size and physical properties and a thicker nanoemulsion (droplet diameter 20-200nm). Nanoemulsion gel is known as nanoemulsion-based hydrogelation by adding an integrated nanoemulsion system to the hydrogel matrix, which provides better skin penetration.[1]

1.1. Nanoemulsion to nanoemulgel

The nanoemulsion technology is the best drug delivery approach to maximise potency and minimise toxicity for most pharmaceuticals. To help them in their hunt for novel and complex dose forms, researchers studied the straightforward administration of medications. A suitable surfactant or co-surfactant with an acceptable HLB value is added to the two immiscible liquids (oil and water) to create a homogenous solution, which is what the nanoemulsion system is made of. Between 10 and 100 nm is where this thermodynamically stable system is located. The many compartments of a stabilised nanoemulsion are depicted in Figure 1. By speeding up the processing of medications in the target area and enhancing their absorption through the skin, nanoemulsion is a viable option for targeting poorly soluble pharmaceuticals and improving the penetration of drug delivery systems.[2]

The physical characteristics of an emulsion are unaffected by the actions of a nanoemulsion that contains nanoscale spheres. However, it has been proven that the therapeutic as a whole is bioavailable. Since first pass metabolism is prevented, it makes sense that the transdermal bioavailability of lacidipine has been studied 3.5 times more than with oral medication. Additionally, nanoemulsion enhances drug penetration through the skin, which engages the interests of researchers. Additionally, the more medication that can be added to the mixture, which improves the thermodynamics towards the skin, the smaller the particle size. Skin

penetration is improved by the medication's affinity for partitioning. Nile red (NR) dye loaded in lecithin nanoemulsion was reported to enter the skin 9 times more effectively than NR-loaded general emulsion in one study. Ethyl oleate and propylene glycol, two other ingredients in the mixture, also encourage permeability. Transdermal medication distribution is most severely hindered by the stratum corneum, a tissue layer that is 10–20 mm thick and has a well-organized, well-composed lipid/protein matrix. The bioavailability of lipophilic flurbiprofen in nanoemulsion is increased by 4.4 times when applied topically compared to oral dosage, according to a recent study.[3]

Because of this, the nanoemulsion is a spontaneous emulsifying technique that performs better than polymeric nanoparticles and liposomes in many respects, including cheaper guidance costs, more hydrophilic and lipophilic drug loading systems, and longer shelf lives while healing agents are conserved.

2. Nanoemulgel:

The introduction of a nanoemulsion that is wholly based on hydrogel is made possible by the incorporation of the nanoemulsion machine intergraded into the hydrogel matrix, or nanoemulgel. Skin penetration is enhanced consequently. Scientists have concentrated their efforts on this nanoemulgel combination in order to develop several drugs that may be used to treat a variety of skin disorders.

As demonstrated in Table 1, emulgel is not a brand-new formulation type and is currently available on the market.

Table 1: Emulgel product available on the market today

S. N.	Product Name	Manufacturer	Active Ingredients
1	Reumadep Emulgel	ErbozetaEnergia Verde	Arnica, Ashwagandha, Myrrh, Ginger, Rosemary, Cloves, Mint.
2	Emulgel Levorag Monodose	THD LAB Farmaceutici	
3	Voltaren Emulgel	Novartis Consumer Health	Propylene glycol, 100 g Diclofenac diethylamine equivalent to 1 g diclofena sodium Base: An aqueous gel fatty emulsion containing isopropanol and propylene glycol.
4	Meloxic Emulgel	Provet	Meloxicam
5	Coolnac Gel Emulgel 1 %	Chumchon	Diclofenac Diethylammonium
6	Benzolait AzEmulgel	Rordermal	Benzoylperossido 10%
7	Miconaz-H-emulgel	Medical Union Pharmaceuticals	Miconazole nitrate, Hydrocortisone
8	Voveron Emulgel	Novartis Pharma	Diclofenac diethyl amine
9	Diclobar emulgel	Barakat pharma	Diclofenac diethyl amine

10	Levorag emulgel	THD Ltd	Hibiscus, liqourice and natural extracts

The nanoemulgel formulation of the topical delivery system acts as a drug reservoir, influencing the rate at which drugs are delivered to the skin from the internal phase. These release processes are influenced by the network's polymer chain composition and crosslink density.[4] Furthermore, a drug's ability to penetrate the skin and successfully release the therapeutic agent is determined by its ability to diffuse out of the vehicle and penetrate through the barrier.

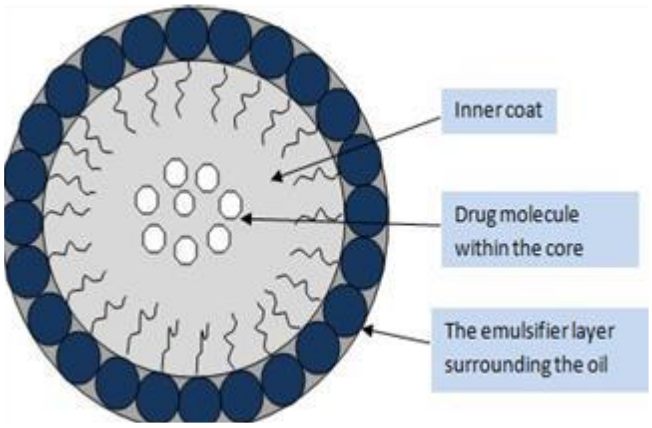


Figure 1: Diagram of Stabilized Nanoemulsion.

The insertion of a nanoemulsion system intergraded into gel matrix results in the formation of nanoemulgel, which incorporates nanoemulsion in a gel basis and increases skin penetration.[5] The mixing of nanomulgels, which serve as drug reservoirs, affects drug release from the inner to the outer phase and beyond. When nanoemulgel is applied to healthy skin, oil droplets are produced, which move through the skin's SC and transport medicine to the desired location. The medication's increased solubilization in the oil phase results in a wider concentration gradient toward the skin, which improves drug penetration into the skin. Nanoemulsion gels attach very effectively. Patient compliance is strengthened further by the higher sparing ability in comparison to creams and ointments and the lower stickiness.

2.1. Advantage: Nanoemulgels have several advantages over other topical formulations that have been researched, including the following:[6-7]

a) Avoid first pass metabolism.
b) Patient-friendly.
c) Appropriate for self-medication.
d) Offer local medicine delivery services.
e) Simple medication discontinuation.
f) Easily suitable for the surroundings surrounding skin.
g) Established effectiveness for a sustained and regulated medication delivery method.
h) The nanoemulsion's stability is influenced by the drug's affinity for the oil, which is enhanced by the dispersion of oil droplets in the gel basis.
i) A strong concentration gradient that increases medication penetration as it descends is also produced by a strong solubilizing power and good skin adhesion.

j) These formulations also improve patient compliance and aid in the distribution of lipophilic and insufficiently water-soluble medications.
k) Furthermore, the nanoemulgel facilitates regulated, shorter-half-life drug release.
l) Provide a formulation that is easier to spread than creams.
m) Nanoemulgels are both non-toxic and non-irritating.
n) superior drug loading compared to other formulations.

3. Rational

There are numerous drawbacks to topical dose formulations such cream, lotion, and ointment. One of these is stickiness, which causes issues for patients during application and has poor spreading qualities and requires rubbing. Additionally, several issues with formulation stability for hydrophilic drugs were found. Due to these issues with most semisolid preparations, both pharmaceutical and cosmetic preparations have increased their use of gelled formulation. Gel is a colloid that contains 99% liquid and is made up of a macromolecular network of fibres made of a substance that gels and liquids that are held in place by surface tension. Despite the benefits, delivering hydrophobic medicines is a significant challenge. To get around this issue, a gel-based system can integrate a lipophilic medicinal moiety via an emulsion-based approach.[8]

4. An essential component of nanoemulgel:

a) Oil: Mineral oils are usually used in nanoemulsions as the medication delivery method. For instance, several fixed oils (cottonseed oil, maize oil, arachisoil, etc.), as well as olive oil, coconut oil, eucalyptus oil, rose oil, clove oil, and many more.[9]

b) Aqueous Phase: When creating nanomulsions and hydrogels, distilled water is commonly used in the aqueous phase.

c) Surfactant and Co-Surfactant: These chemicals are utilised to provide emulsification during the production process as well as to control daily stability during the shelf life of Nanoemulsions generated. The general surfactant choice is determined by the kind of emulsion.[10] Eg: Transcutol, Captex, and Cam d, Span 80, Tween 80, Labrafil, Sodium stearate.

d) Gelling Agent: Gels may be formed with the help of certain polymers called gelling agents, which provide the necessary framework for gel formation. As an example, cellulose derivatives like agar and tragacanth may be found among synthetic and semi-synthetic materials.

e) Permeation Enhancers: These compounds interact with certain skin components to enhance permeability temporarily, which may then be reduced. They might be able to do this with the help of one or more tactics., like

i. destroying the SC's compact structure.
ii. Adding more drugs, cleaners, or co-partition enhancers to the SC.
iii. A protein that engages in cell-to-cell communication.

Focusing on structural modifications in proteins or solvent swelling is the first step in developing a new polar route. This will allow you to construct a new polar route. Some enhancers increase the protein's accessibility in the secretory compartment (SC), whilst other

enhancers enter via the multilaminate route and influence the whole system. They could make it easier for the body to absorb drugs via the proteins in the skin. The shape of the enhancer has a major influence on the procedures that are used in manufacture. There are several examples, some of which include eucalyptus oil, oleic corrosive, isopropyl myristate, lecithin, and chenopodium.[11]

5. Method of formulation

The following steps are involved in making a nanoemulsion-gel:

a) Component screening;
b) Nanoemulsion preparation.
c) Creating Nanoemulgel

By over-adding the medication to various components and then continuously whirling for 72 hours to reach equilibrium, drug solubility in various oils was examined. After centrifuging the samples, the supernatant was collected, and the solubility was assessed using the correct analytical techniques. The most drug-soluble excipients in each category are then further investigated.[12]

a) The psedoternary phase diagram: Depicts different surfactant and cosurfactant mixing ratios (N_{mix}) (2:1, 3:1 and 5:1). Each ratio was created for a study on phase diagrams with an increasing ratio of surfactant to cosurfactant. The dilution medium in this case is aqueous phase (distilled water). In numerous vials, oil and N_{mix} were mixed in various ratios ranging from 9:1 to 1:9. The primary purpose of the research is to build phase boundaries such that they may be found on diagrams. The titration method was employed to create it, with water acting as the aqueous medium. By carefully titrating Oil and N_{mix}, the transparency of the Nanoemulsion may be visually checked. The state of the nanoemulsion is represented by the aqueous phase, oil, and N_{mix} (surfactant and co-surfactant) axes, respectively.[13]

b) Preparation of Nanoemulsion: A specific medication is first dissolved in oil and then added to a mixture called N_{mix} to create a nanoemulsion of that medication. Water is then used to dilute this combination.

c) Preparation of Nanoemulgel: To make gel basis, one gramme of carbopol is dissolved in the required volume of water. The created nanoemulsion is progressively added while stirring after the carbopol solution has completely swollen and dispersed for 24 hours. The inclusion of triethanolamine produces a consistent gel dispersion. Finally, distilled water is used to adjust the last necessary component (Figure-2).

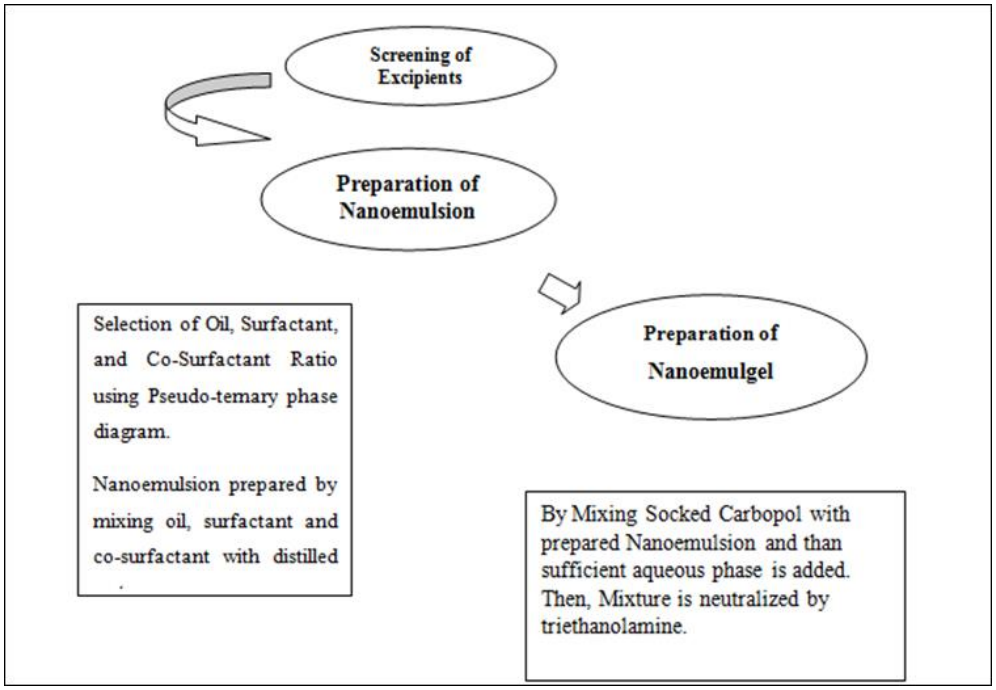


Figure 2: A Flowchart for Nanoemulgel formulation preparation

6. Optimization and evaluation:

a) pH measurement: A pH metre revealed that some topical treatments had pH values between 5 and 6. For testing, 1 gramme of gel is dissolved in 10 millilitres of water. The pH of each formulation is examined three times to avoid mistakes.[14]

b) Size of globules: 1.0 grams of gel were dissolved in water and agitated to ensure dispersion prior to placing the sample into the Malvern zetasizer's photocell to measure globule size.

c) Swelling Index: 10 ml of 0.1N NaOH solutions are combined with 1 gram of topical nanoemulgel that has been applied to porous aluminum foil. A sample is taken every so often, and the weight is recorded until there is no change in weight.:

Swelling Index (SW) % = [(Wt-Wo)/Wo]*100

Where (SW) % is the percentage of swelling, and Wo is the original weight of the nanoemulgel, and Wt is the weight of the swollen nanoemulgel at t.

6.1. Measuring the strength of bio adhesives: One glass slide was fastened to each of the apparatus's arms, and these slides were sandwiched between two more glass plates. The additional weight is added using only one plate. An exact one gramme of nanoemulgel is placed in the middle of two slides that contain samples of hairless rate skin. It is possible to separate two glass slides that have been sandwiched together by applying pressure to only one of the slides. After then, an additional 200 milligrammes of weight is added each minute until the surface of the skin begins to crack. The strength of the bio adhesive was determined by determining the amount of weight necessary to detach the nanoemulgel from the skin. The formula that is used to determine it is as follows:

Bio adhesive Strength = W / A

Where, W is the required weight in grams and A is the area (cm2)

6.2. Rheological features identification: Using a Brookfield viscometer with spindle number S64, the thickness of 20 grammes of Nanoemulsion-gel that was contained inside of a beaker that held 25 millilitres was determined.[15]

6.3. Accelerated stability studies: The formulations are maintained in an oven for three months at 37°C, 45°C, and 60°C, according to ICH standards. Every two weeks, the drug content is tested using an appropriate analytical technique. The premise for determining stability is a change in gel pH or drug breakdown.[16]

a) **Determination of % drug content:** To calculate the drug content %, 25 ml of methanol and 1 gramme of Nanoemulgel are combined. It goes through a 30-minute sonication. The analytical approach given in this solution was used to calculate the drug content.

6.4. Spread-ability of Gellifed Nanoemulgel: It may be calculated using the Mutimer-recommended Slip and Drag basis. A glass slide of comparable size is sandwiched in this image between the bottom ground slide, which is attached with a wooden block and 2 gm of Nanoemulgel, and the top ground slide, which is fastened with a hook and 500 ml of weight.[16] More pressure was put on the pan connected to the second slide after five minutes. By timing how long it took the upper slide to advance 5 cm and then using the following calculation, the spreadability was determined:

$$\textbf{Spreadability (S) = M*L / T}$$

Where, M is the upper slide's weight, L is the length of the glass slides, and T is the time it takes for the upper slide to cover the distance.

6.5. Test for skin irritability: 0.25gm Each individual location is treated with nanoemulgel (there are two sites per rabbit). A change in skin tone or an unfavourable alteration in morphology is detected and verified after 24 hours of therapy.

6.6. Studies on in vitro diffusion: Franz diffusion cells are used to investigate the diffusion of synthesised nanomeulgel. In the experiment, 0.5 grams of the sample are adhered to a cellophane membrane. After that, phosphate buffer with a pH of 7.4 is used to conduct the diffusion for eight hours at 37°C.A new buffer solution is added and a 1 ml pg sample is collected after a one-hour pause. The appropriate analytical method is used to analyze the samples that have been collected.[17-18]

6.7. Evaluation of Skin Permeability: The compound and underlying changes in the epidermal layer are evaluated utilizing differential scanning calorimetry (DSC). DSC is utilised to determine the penetration process by analysing temperature transitions in rat desiccated SC membranes. Skin samples from the treated and untreated groups were first hydrated for at least 48 hours in a 27% sodium-br solution to ensure 20% hydration. Prior to examination, the skin samples are kept on silica gel in desiccators for three days. The skin sheets are cut into 4 mg weighted pieces and placed in sealed 10 L aluminium pans with an empty pan for comparison before being loaded into the differential scanning calorimetry machine.[19-22]

7. Major challenges for the nanoemulgel drug delivery system:

a) The nanoemulgel drug delivery system, while its obvious benefits, nonetheless confronts a variety of challenges, from the manufacturing process to stability-related issues. The most important step in creating a nanoemulgel requires a significant amount of energy during nanoemulsion preparation.[23]
b) Despite the fact that there aren't many low-energy manufacturing processes, those that do frequently need more surfactants and aren't completely suitable for mass production. Excessive surfactant uses causes skin irritation and contact dermatitis.[24]
c) Most frequently, nanoemulsions just need to be made before usage. Another critical problem is the gel phase's stability. Most substances that gel are extremely pH and temperature sensitive. For instance, the frequently used gelling chemical carbopol needs a narrow pH range to exhibit gelling capabilities. It loses its ability to gel and may even break at pH levels that are above or below that range. The pH of the preparation may fluctuate as a result of the leaching of acidic or alkaline components from the storage container, which might lead to the gel being unstable. Temperature changes that can place when the product is being kept might cause the gel to break. Once more, a crucial step is the inclusion of the nanoemulsion into the gel. While low speed stirring is unable to create a homogeneous or uniform mixture, high speed churning is able to dissolve the gel. To ensure the optimum stability of the nanoemulgel formulation, the right kind and quantity of surfactant and co-surfactant must be used.[24]
d) Rare instances of allergic skin reactions to nanoemulgel exist. The limited selections of surfactants and co-surfactants that can be used to make nanoemulsions represent a substantial additional problem. With an average molecular weight of more than 400 Dalton, nanoemulgel compositions are too big for large drug molecules to enter the skin. Another noteworthy problem is the difficulty of the nanoemulsion phase of nanoemulgel to maintain stability over an extended period of time. Oswald ripening can occasionally lead to nanoemulsion instability because of the tiny emulsion droplets it produces.[25]

8. Improvement in pharmacodynamic activity:

Researchers have conducted and reported comparative studies of pharmacological activity of drugs using different testing paradigms (Table-2). Some recent studies with notable findings are discussed below.

a) According to the findings of Jeengar and colleagues, a curcumin-based nanoemulgel with 0.5% weight-to-weight curcumin was more successful in treating rat paw edoema than a normal curcumin gel containing 14.22% curcumin. The utilisation of nanoemulgel therapy resulted in a quicker reduction in the increased spleen weight that was generated by the imiquimod treatment. This was in comparison to the utilisation of pharmaceutical solution or commercial solution, both of which resulted in a slower reduction in the increased spleen weight.[26]
b) The anti-inflammatory activity of a commercially available gel formulation was compared with a betamethasone dipropionate nanoemulsion gel formulation developed by Alam *et al*. in rats. The group treated with nanoemulgel had the highest level of

activity. Compared with the commercial formulation (40.97%), the nanoemulsion gel therapy significantly reduced edema (77.83%) after 24 hours.[27]

c) The antifungal activity of the Mahtab *et al*., nanoemulgel ketoconazole formulation is superior to that of the solution. After 48 hours, the nanoemulsion was mixed into the solution (22.4 mm for T. rubrum, C. albicans). The effectiveness of the antifungal may be due to the small size and the slow release of ketoconazole into the medium.[28]

d) Researcher Eid *et al*. investigated the possibility that a nanoemulgel containing oil from Swietenia macrophylla may stop carrageenan from causing edoema to form in the paws of rats. It turned out that the pharmacological technique was not nearly as successful as the nanoemulsion technology. It is probable that the dip in activity was caused by the nanoscale size of the oil droplets, which makes mouse skin particularly oil-sensitive. This would explain why the drop-in activity occurred. In such case, we would have an explanation for the phenomena.[29]

e) Radhika and Guruprasad *et al*., investigated the anti-inflammatory impact of flurbiprofen nanoemulsions using the carrageenin-induced rat paw edoema procedure. After 12 hours, the nanoemulsion gel was found to be more effective (Fig. 3) than the standard gel formulation (68.0%) at inhibiting paw edoema (85.2%).[30]

f) It was observed in research that evaluated the antifungal characteristics of various Syamala products that the butenafine included in the nanoemulgel was able to enter the skin of mice more effectively than the cream could. The investigation was carried out in the United States. In order to treat fungal infections, the cream is normally administered to the regions that are afflicted by the condition. The skin of mice affected with fungus showed symptoms of recovery after receiving treatment with nanoemulsion for a period of 12 days, and the cream maintained its effectiveness for a period of 16 days.[31]

g) In human keratinocyte cell lines, we investigated whether leflunomide demonstrated antipsoriatic and antimelanomatous effects. This research was conducted in the city of Pune and its surrounding areas. It was revealed that the activity of leflunomide might perhaps be enhanced by using a nanoemulsion as the vehicle for its manufacturing. This was done via extensive research. Because of the leflunomide nanoemulsion's enhanced permeability, the process of wound healing was accelerated significantly.[32]

h) In rat paw edema caused by carrageenan, Khullar *et al*. investigated the anti-inflammatory effectiveness of topical mefenamic acid emulsions. compared to the diclofenac sodium gel that is sold commercially. Commercial formulations of diclofenac sodium emulsion were proven to have equivalent efficiency and % inhibition of rat paw edema.[33]

i) Prasad and colleagues, in order to evaluate the efficacy and safety of a nanoemulsion gel formulation for adapalene and clindamycin, a clinical trial with 212 human volunteers was conducted. The subjects took part in the study so that the researchers could gather data. The nanoemulsion gel shown a considerable improvement in the decrease of both inflammatory (88.7% vs. 71.4%) and non-inflammatory (74.9% vs. 58.4%) lesions when compared with standard gels. It has been shown that complex nanoemulsion formulations are superior to standard formulations in terms of their

ability to treat acne vulgaris while also causing less irritation to the people using them. An immediate and potent anti-inflammatory impact is produced in the body as a result of the nanoemulsion gel composition. improve the drug's capacity to penetrate the region of the affected joint that is generating the discomfort. It is conceivable that the nanoemulsions, in and of themselves, were the driving force behind the achievement.[34]

j) Nanoemulgel's enhanced pharmacodynamic action in comparison to medications Kurana et al. Figure 4 illustrates it (Khurana *et al.*, 2013). The greater penetration into the skin and systemic circulation compared to other respiratory systems is responsible for the superior pharmacodynamics of various medications supplied by the nanoemulgel delivery method.[35]

k) According to Somagoni *et al*., nanoemulsions reduced ear edema 3.22 times and 2.01 times more, respectively, than drugs and similar products in imiquimod-induced psoriasis-like plaques. Nanoemulgel treatment reduced spleen weight due to imiquimod treatment faster than drug or commercial treatment.[36]

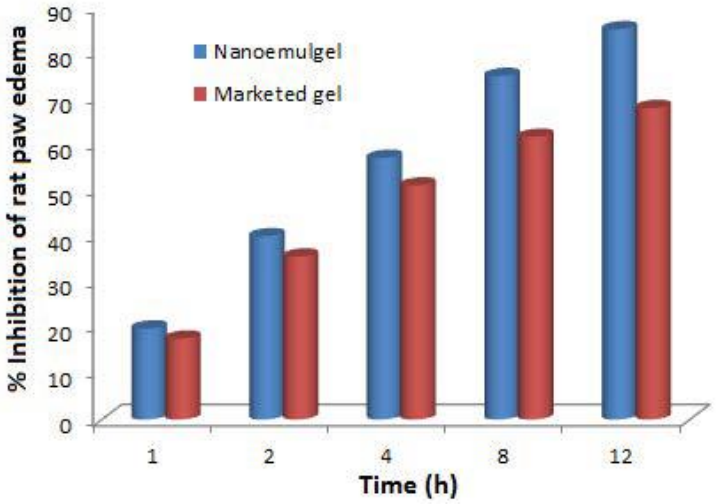


Figure 3. Differentiation plot of the anti-inflammatory effects of commercial gel and flurbiprofen nanoemulgel.

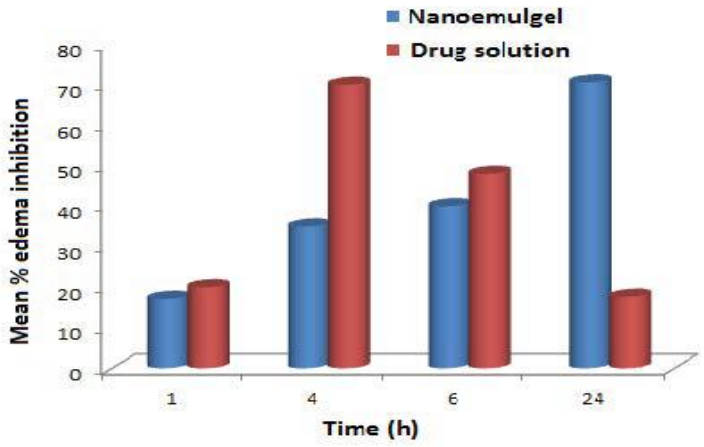


Figure 4. Meloxicam solution and nanoemulgel for the treatment of inflammation: a differentiation plot comparison.

Table 2: Compares experimental results regarding nanoemulgel pharmacological action.

API	**Experimental model**	**Activity**	**Ref.**
Betamethasone dipropionate	Rat paw edema is caused by carrageenan.	Paw volume inhibition (%) after 24 hours: Marketed product: 40.97 Nanoemulgel: 77.83	27
Swietenia *macrophylla* oil	Rat paw edema is caused by carrageenan.	Paw volume inhibition (%) after 4 hours: Nanoemulgel: 69.6 Oil: 16.9	29
Flurbiprofen	Rat paw edema is caused by carrageenan.	Paw volume inhibition (%) after 12 hours: Gel: 68 Nanoemulgel: 85.2	30
Mefenamic acid	Rat paw edema is caused by carrageenan.	*nhibition of paw volume (%):* Diclofenac gel: 65.71 Mefenamic acid nanoemulgel: 55.72	33
Ketoconazole	T. rubrum and C. albicans are targets of in vitro antifungal activity	48-hour incubation zone of inhibition (mm): T. rubrum Drug solution: 22.4 Nanoemulgel: 28.3 *C. albicans* Drug solution: 23.5 Nanoemulgel: 28.1	28
Combination of adapalene and clindamycin	Acne vulgaris on the human face	Mean score for acne severity fell: Gel: 1.4 Nanoemulgel: 1.9	34
Aceclofenac and Capsaicin	Model of psoriatic plaques caused by imiquimod	Score* for PASI: Free 3.55 approximately; 2.70 in the product Nanoemulsion: 0.75	36
Butenafine	Skin fungus infection in rats	Duration of total recovery (days): Cream: 16 Nanoemulgel: 12	31
Leflunomide	keratinocyte cell line from humans	The following formula may be used to determine the needed drug concentration (in mg/ml) to produce a 50% reduction in net protein growth. Gel: >80 Nanoemulgel: <40	32

* PASI stands for Psoriasis Area and Severity Index – Which is used to score the severity of inflammation in rat or experimental model. For five days, the scoring was done every 24 hours.

9. Improvement in pharmacokinetic activity:

To determine how the drug is removed from the formulation, a few investigations on the pharmacokinetic properties of different nanoemulsion formulations have been carried out (Table 3).

a) According to Somagoni *et al.*, the nanoemulgel formulation had a Cmax that was 2.94 and 2.09 times higher than the commercial version did for aceclofenac and capsaicin, respectively. Skin microdialysis was employed in the experiment, which was conducted on rats.[36]

b) A team of researchers led by Singh and with colleagues studied the pharmacokinetic properties of an oral formulation comprising carvedilol nanoemulsion gel. When carvedilol was applied topically rather than taken orally, the AUC0-t value of the drug rose by a factor of 1.72. Following 3 hours of treatment with nanoemulsion gel, the maximum plasma concentration of carvedilol was 3.48 g/ml. This is less than the 4.23 g/ml peak plasma concentration that was reached following two hours of oral tablet treatment. They proposed a relationship between the low Cmax and delayed Tmax of the nanoemulsion gel and the drug's poor skin penetration as the reason for the slow skin penetration of carvedilol. They concluded that the carvedilol topical nanoemulsion gel formulation may be more efficient than the drug's oral tablet form.[37]

c) The bioavailability of telmisartan is improved when the drug is eaten in the form of a nanoemulsion as compared to normal gels, according to the results of a pharmacokinetic research on nanoemulsion formulations conducted by Aparna and colleagues. Comparing the two pill formulations revealed that this was the case. It was shown that when telmisartan was delivered as a nanoemulgel (334.37 g.h/ml) as compared to a conventional gel (221.08 g.h/ml), the area under the plasma concentration curve for the infinite time effect (AUC0-) was larger. Comparing the two distinct medication formulations revealed this to be the case. Telmisaratan's maximum plasma concentration (Cmax) is greater than that of the nanoemulsion gel (5.7 g/ml) and was recorded at 6.2 g/ml. The gel's maximum plasma concentration (Tmax) was obtained following the nanoemulsion (2 h). When lipophilic medicines are combined with nanoemulsion gels, their bioavailability increases.This will promote drug permeability due to the high surfactant content of the nanoemulsion.[38]

d) According to Wais and colleagues' study, glibenclamide's bioavailability is increased by a factor of 3.9 when administered topically as a nanoemulsion gel as opposed to consumed orally. Pharmacokinetic tests revealed that the drug's T_{max} value increased after topical administration, indicating that nanoemulsions were given more time to release slowly. The mean C_{max} following administration of the nanoemulsion was 46.7 ng/ml, which is higher than the C_{max} reached with oral medicine (40.102 ng/ml). This study is crucial because it shows that nanoemulsions are superior than oral treatment in terms of effectiveness. When compared to the variance in plasma concentrations that were obtained after oral delivery, it was shown that the plasma concentration state was present in the nanoemulsion. Following topical application of glibenclamide nanoemulsions, the plasma concentration-time curve (AUC0-t) values were approximately four times higher than the oral control (426.37 ng/h/ml). A comparison

between the oral control and the topical treatment must be done in order to arrive at these figures. do. This suggests that nanoemulsion formulations instead of solutions may be used for a larger variety of pharmaceuticals.[39-40]

All these investigations came to the conclusion that the nanoemulgel formulation's embedded medication had a superior pharmacokinetic profile.

Table 3: Compares experimental results regarding nanoemulgel pharmacokinetic action.

S.N.	API	Composition of formulation	Pharmacokinetic data	Ref.
1.	Carvedilol	Oleic acid + IPM in oil (3:1) Tween 20 surfactant, Carbitol co-surfactant, Carbopol-934 gelling agent	*Cmax (g/ml): Oral: 37.09, Nanoemulgel: 63.89 Tmax (h): Oral: 4.23, Nanoemulgel: 3.48 2 oral, 12 nanoemulgel*	37
2.	Aceclofenac and Capsaicin	miglyol and olive oil (1:1), Polysorbate 80 (surfactant), Transcutol (Co-surfactant), Propylene glycol (gelling agent).	*Cmax of aceclofenac (g/ml) 8.94 for the marketed product, 26.24 nanoemulgel, Aceclofenac Tmax (h): Product number: 14, 18 nanoemulgel, Capsaicin Cmax (g/ml): 0.047 (marketed product), 0.098 for nanoemulgel, Tmax (h) of capsaicin: marketed product: 12, 18 nanoemulgel*	36
3.	Telmisartan	Labrafil oil Acrysol (surfactant), Carbitol (co-surfactant). Carbopol (gelling agent).	*Gel: 221.08, Nanoemulgel: 334.37; AUC0- (g.h/ml); Cmax (g/ml); Nanoemulgel: 6.2 Tmax (h), Gel: 5.7 8 gels, 2 nanoemulgels*	38
4.	Glibenclamide	Labrafac with triacetin (1:1) (Oil), Tween 80 (Surfactant), Monoethyl ether glycol, diethylene (Co-surfactant), 934 Carbopol (Gelling agent)	*Oral: 40.102 ng/ml, Nanoemulgel: 46.7 AUC0-: 442.396 ng/h/ml, Nanoemulgel: 1941.121 Tmax (h): Oral: 2 ng/ml, Nanoemulgel: 12*	39

10. Conclusion:

It has been shown that nanoemulgels are a great choice for usage as a mechanism for the administration of medication because they are both efficient and convenient. This is one of the

reasons why they are a good alternative. This new formulation, in contrast to past iterations, has properties that make it less difficult for patients to swallow their prescribed medication as directed. These qualities include a consistency that is like that of a gel and the lack of a base that is oily. Specifically, the absence of an oily basis. In addition to this, the fact that the drug does not have an oily base is another factor that adds to its improved efficacy. By incorporating nanoemulsion into the gel matrix, it is feasible to convert formulations into systems that allow for dual control of their release. This not only improves spareability, but it also removes frequent emulsion difficulties like creaming and phase separation. In other words, it is a win-win. In order to treat a wide range of skin disorders more effectively, it has been shown that making use of a gel that is comprised of nanoemulsions is optimal. It is conceivable that in the not-too-distant future, formulations that are based on nanoemulsion-gel will offer a route of administration of hydrophobic medications that is both more predictable and effective. This is because nanoemulsion-gel can be made to behave like a gel. Many of the topical medications that are used to treat skin infections are formulated with components that provide water resistance, which is a desirable quality in topical treatments. Because these medications are added to the oil phase of the nanoemulsion before the addition of the gel base, it is possible that they may be administered as nanoemulgels in a manner that is both effective and safe. In the not-too-distant future, there is a good chance that nanoemulgel will take over as the dominant method for the delivery of lipophilic medications via the topical route. The nanoemulgel strategy has a strong possibility of becoming the major method, despite the fact that there are a few obstacles that need to be addressed.

Conflict of Interest; The authors declare that the review was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

Acknowledgement: The authors are thankful to his/her parents.

Funding: None.

Ethics approval and consent to participate: Not applicable.

Human and animal rights: Not applicable.

Consent for publication: Not applicable.

Code availability: Not applicable.

List of Abbreviations:

Abbreviation	Full Form
µm	Micron meter
nm	Nanometre
mg	Milligram
g	Gram
HLB	Hydrophilic lipophilic balance
%	Percentage
SC	Secretory compartment
DSC	Differential scanning calorimetry
C_{max}	Maximum concentration
AUC	Area under curve
°C	Degree Centigrade

L	litter
ng/ml	Nanogram per millilitre
T_{max}	Transport maximum
g/ml	Gram per millilitre
h	Hours
N_{mix}	surfactant and co-surfactant

References:

1. Lieberman, H.A., M.M. Rieger, and G.S. Banker, Pharmaceutical Dosage Forms Disperse Systems Emulsion and Microemulsions, 2014(2), 335-369.
2. Chellapa P, Mohamed AT, Keleb EI, Elmahgoubi A, Eid AM, Issa YS, Elmarzugi NA. Nanoemulsion and nanoemulgel as a topical formulation. IOSR J Pharm. 2015 Oct;5(10):43-7.
3. Marti-Mestres G, Nielloud F. Emulsions in health care applications—an overview. Journal of dispersion science and technology. 2002 Jan 1;23(1-3):419-39.
4. Singh RP, Parpani S, Narke R, Chavan R. Emulgel: A recent approach for topical drug delivery system. Asian Journal of Pharmaceutical Research and Development. 2014 Mar 1:112-23.
5. Jain A, Deveda P, Vyas N, Chauhan J, Khambete H, Jain S. Development of antifungal emulsion based gel for topical fungal infection (s). IJPRD. 2011;2(12):18-22.
6. Verma S, Singh AK, Mukharjee A. Formulation and evaluation of ketoconazole nanoemulgel. World journal of pharmacy and pharmaceutical sciences. 2016;5(2):899-911.
7. Joshi B, Singh G, Rana AC, Saini S, Singla V. Emulgel: a comprehensive review on the recent advances in topical drug delivery. Int Res J Pharm. 2011;2(11):66-70.
8. Pant S, Badola A, Baluni S, Pant W. A review on emulgel novel approach for topical drug delivery system. World journal of pharmacy and pharmaceutical sciences. 2015;4(10):1728-43.
9. Montenegro L, Carbone C, Condorelli G, Drago R, Puglisi G. Effect of oil phase lipophilicity on in vitro drug release from o/w microemulsions with low surfactant content. Drug development and industrial pharmacy. 2006 Jan 1;32(5):539-48.
10. Savale SK. A review-self nanoemulsifying drug delivery system (SNEDDS). International Journal of Research in Pharmaceutical and Nano Sciences. 2015;4(6):385-97.
11. MORTAZAVI SA, ABOU FAZELI R. An investigation into the effect of various penetration enhancers on percutaneous absorption of piroxicam.
12. Alexander A, Khichariya A, Gupta S, Patel RJ, Giri TK, Tripathi DK. Recent expansions in an emergent novel drug delivery technology: Emulgel. Journal of Controlled Release. 2013 Oct 28;171(2):122-32.
13. Zignani M, Tabatabay C, Gurny R. Topical semi-solid drug delivery: kinetics and tolerance of ophthalmic hydrogels. Advanced drug delivery reviews. 1995 Aug 1;16(1):51-60.
14. Kikwai L, Babu RJ, Prado R, Kolot A, Armstrong CA, Ansel JC, Singh M. In vitro and in vivo evaluation of topical formulations of spantide II. Aaps Pharmscitech. 2005 Dec;6(4):E565-72.
15. Shokri J, Azarmi S, Fasihi Z, Hallaj-Nezhadi S, Nokhodchi A, Javadzadeh Y. Effects of various penetration enhancers on percutaneous absorption of piroxicam from emulgels. Research in Pharmaceutical Sciences. 2012 Oct;7(4):225.

16. Mohamed MI. Optimization of chlorphenesin emulgel formulation. The AAPS journal. 2004 Sep;6(3):81-7.
17. Shankar R, Tiwari V, Mishra C, Singh C, Sharma D, Jaiswal S. Formulation and evaluation of ketoconazole nanoemulsion gel for topical delivery. American Journal of Pharmtech Reseatch. 2015;5(5):446-62.
18. Modi JD, Patel JK. Nanoemulsion-based gel formulation of aceclofenac for topical delivery. International Journal of Pharmacy and Pharmaceutical Science Research. 2011;1(1):6-12.
19. Bonacucina G, Cespi M, Palmieri GF. Characterization and stability of emulsion gels based on acrylamide/sodium acryloyldimethyl taurate copolymer. Aaps Pharmscitech. 2009 Jun;10(2):368-75.
20. Masmoudi H, Piccerelle P, Le Dréau Y, Kister J. A rheological method to evaluate the physical stability of highly viscous pharmaceutical oil-in-water emulsions. Pharmaceutical research. 2006 Aug;23(8):1937-47.
21. Tanwar YS, Jain AK. Formulation and evaluation of topical diclofenac sodium gel using different gelling agent. Asian Journal of Pharmaceutical Research and Health Care. 2012;4(1).
22. Shakeel F, Baboota S, Ahuja A, Ali J, Shafiq S. Skin permeation mechanism of aceclofenac using novel nanoemulsion formulation. Die Pharmazie-An international journal of pharmaceutical sciences. 2008 Aug 1;63(8):580-4.
23. Sharma, N., Bansal, M., Visht, S., Sharma, P., & Kulkarni, G. (2010). Nanoemulsion: A new concept of delivery system. *Chronicles of Young Scientists*, *1*(2), 2–6.
24. Bhavesh S, Shah CN. Nanoemulgel: a comprehensive review on the recent advances in topical drug delivery. Pharma Sci Monit. 2016;7(2):346-55.
25. Gutiérrez JM, González C, Maestro A, Solè IM, Pey CM, Nolla J. Nano-emulsions: New applications and optimization of their preparation. Current opinion in colloid & interface science. 2008 Aug 1;13(4):245-51.
26. Jeengar, M. K., Rompicharla, S. V. K., Shrivastava, S., Chella, N., Shastri, N. R., Naidu, V.G. M., & Sistla, R. (2016). Emu oil based nano-emulgel for topical delivery of curcumin. *International Journal of Pharmaceutics*, *506*(1–2), 222–236.
27. Alam, M. S., Ali, M. S., Alam, N., Alam, M. I., Anwer, T., Imam, F., Shamim, M. (2012). Design and characterization of nanostructure topical gel of betamethasone dipropionate for psoriasis. *Journal of Applied Pharmaceutical Science*, *2*(10), 148–158.
28. Mahtab, A., Anwar, M., Mallick, N., Naz, Z., Jain, G. K., & Ahmad, F. J. (2016). Transungual Delivery of Ketoconazole Nanoemulgel for the Effective Management of Onychomycosis. *AAPS PharmSciTech*, *17*(6), 1477-1490.
29. Eid, A. M. (2014). Preparation, Characterization and Anti-Inflammatory Activity of Swietenia macrophylla Nanoemulgel. *Journal of Nanomedicine & Nanotechnology*, *5*(2), 1-10.
30. Radhika, P. R., & Guruprasad, S. (2016). Nanoemulsion Based Emulgel Formulation of Lipophilic Drug for Topical Delivery. *International Journal of PharmTech Research*, *9*(6), 210–223.
31. Syamala, U. (2014). Development & Optimization of Allyl Amine Antifungal Nanoemulgel Using 23 Factorial Design: for the Treatment of Tinea Pedis. *European Scientific Journal*, *4*(12), 597–605.
32. Pund, S., Pawar, S., Gangurde, S., & Divate, D. (2015). Transcutaneous delivery of leflunomide nanoemulgel: Mechanistic investigation into physicomechanical characteristics, in vitro anti-psoriatic and anti-melanoma activity. *International Journal of Pharmaceutics*, *487*(1–2), 148–156.

33. Khullar R, Kumar D, Seth N, Saini S. Formulation and evaluation of mefenamic acid emulgel for topical delivery. Saudi pharmaceutical journal. 2012 Jan 1;20(1):63-7.
34. Prasad S, Mukhopadhyay A, Kubavat A, Kelkar A, Modi A, Swarnkar B, Bajaj B, Vedamurthy M, Sheikh S, Mittal R. Efficacy and safety of a nano-emulsion gel formulation of adapalene 0.1% and clindamycin 1% combination in acne vulgaris: A randomized, open label, active-controlled, multicentric, phase IV clinical trial. Indian Journal of Dermatology, Venereology and Leprology. 2012 Jul 1;78(4):459.
35. Khurana S, Jain NK, Bedi PM. Nanoemulsion based gel for transdermal delivery of meloxicam: physico-chemical, mechanistic investigation. Life sciences. 2013 Mar 14;92(6-7):383-92.
36. Somagoni, J., Boakye, C. H. A., Godugu, C., Patel, A. R., Faria, H. A. M., Zucolotto, V., & Singh, M. (2014). Nanomiemgel - A novel drug delivery system for topical application - In vitro and in vivo evaluation. *PLoS ONE*, *9*(12), 1–30.
37. Singh, B. P., Kumar, B., Jain, S. K., & Shafaat, K. (2012). Development and characterization of a nanoemulsion gel formulation for transdermal delivery of carvedilol. *International Journal of Drug Development and Research*, *4*(1), 151–161.
38. Aparna, C., Srinivas, P., & Patnaik, K. S. K. R. (2015). Enhanced Transdermal Permeability of Telmisartan By a Novel Nanoemulsion Gel. *International Journal of Pharmacy and Pharmaceutical Sciences*, *7*(4), 335–342.
39. Wais, M., Samad, A., Nazish, I., Khale, A., Aqil, M., & Khan, M. (2013). Formulation development ex-vivo and in-vivo evaluation of nanoemulsion. *International Journal of Pharmacy and Pharmaceutical Sciences, 5*, 747-754
40. Sengupta P, Chatterjee B. Potential and future scope of nanoemulgel formulation for topical delivery of lipophilic drugs. International journal of pharmaceutics. 2017 Jun 30;526(1-2):353-65.