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A Update on Topical Drug Delivery system Nanoemulgel

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ABSTRACT
When compared to other formulations, nanoemulgel, a potential transdermal delivery vehicle, has exhibited exceptional improvements for lipophilic medicines. Many current medications have lipophilic characteristics, which causes concerns such as low oral bioavailability, variable absorption, and pharmacokinetic fluctuations. As a result, this unique transdermal delivery technique provides significant benefits over traditional oral and topical medication administration approaches, minimising these problems. The category of oil-in-water nanoemulsions includes specialised formulations known as nanoemulgels. They possess a non-greasy gel-like consistency that is created by adding gelling chemicals. In addition to improving user compliance, this gel phase significantly contributes to product stabilisation by lowering surface and interfacial tension. Additionally, it makes precise site-of-action targeting possible, effectively avoiding first-pass metabolism. As a result, consumers are freed from worries about stomach problems and systemic compatibility. This succinct review digs into the benefits of nanoemulgel as an improved topical drug delivery method, including a study of its ingredient screening, formulation procedures, and the most recent advances in pharmacokinetic and pharmacodynamic research undertaken by experts worldwide. Finally, our study highlights the potential of nanoemulgel as a more efficient method of administering medications topically.

I. INTRODUCTION

Nanoemulgel is a combination of a nanoemulsion and a gel system, two distinct systems. Oil-in-water or water-in-oil nanoemulsions may be used as a delivery system for drugs. The origins of pharmaceutical culture may be traced back to Mesopotamia (2600 BC), when water and plants were used to heal different diseases. This marked the start of a path towards the creation of contemporary dosing systems. Numerous routes of administration have arisen in the domain of pharmaceutical research to ease the delivery of modern dosage forms. The choice of these forms is mostly determined by the physicochemical properties of the active chemicals. Lipophilic properties have recently dominated the synthesis and development of pharmacological drugs.[1] Surprising data studies have shown the widespread problem of poor aqueous solubility among novel chemical entities, with rates reaching 70%, much beyond early findings of roughly 40% with solubility issues. The lipophilic properties of these recently produced medications present a number of issues, including inferior oral bioavailability, irregular absorption, individual differences in pharmacokinetics, and a lack of dosage proportionality.[2]

An ongoing and continual formulation strategy is required to address these challenges and concentrate on improving solubility. Pharmaceuticals that are poorly soluble may be made more soluble by using a variety of techniques, including physical and chemical adjustments as well as the development of novel formulations (see Fig. 1).[3] Particle size reduction for possible distribution through nanocarrier systems, crystal engineering, creating amorphous formulations, and the use of various lipid-based tactics are just a few of the formulation techniques that have been investigated. As a result, multiple routes of administration for these formulations have been investigated, taking into account their unique advantages and disadvantages, the targeted site of action, the severity of the disease, the age and condition of the patients, the availability of dosage forms, and, ultimately, user compliance. Because of its alignment with patient compliance, the oral route is the most preferred technique. However, oral treatment often results in hepatic first-pass metabolism, needing greater doses.[4] Furthermore, the inclusion of surfactants in lipid-based formulations might be a substantial disadvantage owing to the risk of gastrointestinal discomfort. Furthermore, the drug's systemic dispersion throughout the body may result in

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unforeseen adverse effects. To avoid these unfavourable hurdles, topical medication administration appears as a noninvasive, painless, and nonirritating option.[5] This strategy has a number of advantages, including precise drug delivery to the targeted area, enhanced drug release from the formulation to improve percutaneous absorption, avoidance of first-pass metabolism and gastrointestinal problems, localised action with few systemic side effects, and, under certain conditions, increased bioavailability achieved through an extended release pattern.[6]

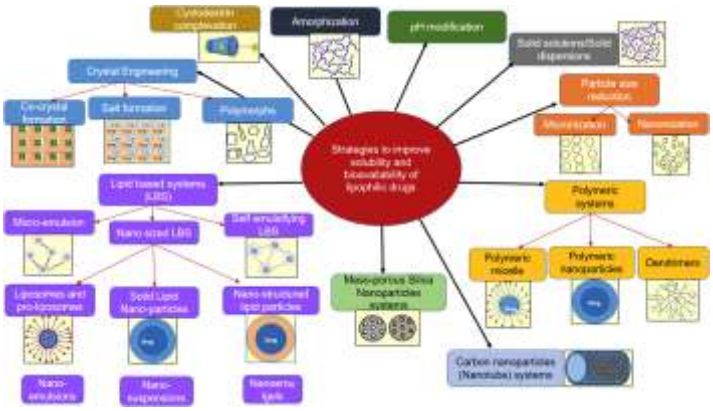

Fig 1. increase the bioavailability of medicines with low water solubility.

Ointments and other conventional transdermal preparations, creams, and lotions, have various problems, including stickiness, poor spreadability, stability concerns, and, ultimately, low patient compliance. Transdermal administration has been modernised via novel formulations, resulting in clear gels and emulgels with increased compliance and efficiency with patients.[7] As a consequence, these formulations are becoming more and more well-liked in the pharmaceutical and cosmetic industries. Despite the various benefits of gel and emulgel formulations, hydrophobic drug delivery remains a serious barrier. Furthermore, researchers are concerned with medication penetration through the stratum corneum in order to assure systemic action in transdermal administration. According to the literature, nanosized topical formulations may improve active chemical permeability by breaking.[8] The lipid bilayer displays distinct voids and vacant spaces in skin samples treated with nanoemulsions. Nanoemulsions exhibit significant potential due to their isotropic and see-through (or semi-transparent) heterogeneous nature.[9]

Despite its many benefits, nanoemulsion's topical use is hampered by its poor viscosity and spreadability. Researchers addressed these problems by transforming nanoemulsions into nanoemulgels. Nanoemulgels are made by introducing a gelling agent into an oil-in-water (o/w) or water-in-oil (w/o) nanoemulsion, resulting in a gel-like consistency with better nanoemulsion characteristics for transdermal application. alternative advantages of nanoemulgels for topical distribution include less skin irritation, higher permeability. This colloidal delivery technique may be used to integrate medicinal molecules, hence increasing bioavailability, stabilising medication levels, and decreasing adverse effects.[10] Nanoemulsions promote optimal medication localization and dispersion, allowing for percutaneous absorption inside the skin to improve local effectiveness and, where necessary, systemic effects. They can even traverse the difficult blood-brain barrier, giving them an edge in central nervous system function. Studies on nanoemulgels are expanding to include a wide range of delivery systems, such as As interest among researchers, patient acceptability, and promising research findings in the area of pharmaceutical formulation development rise, it is anticipated that transdermal, dental, vaginal, ophthalmic, and nasal-to-brain nanoemulgels will be used to treat a variety of local and systemic disorders.[11]

Formulation Components Consideration

An oil phase and an aqueous phase are combined to create an o/w or w/o nanoemulsion. a thin surfactant coating that is sometimes strengthened by the addition of cosurfactant, enervates the tiny dispersed phase. The next section provides an overview of oil selection techniques that take use of various integrating oil qualities.[12]

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Oil section

The lipid component, more precisely the oil, is one of the essential parts of nanoemulgels. It is crucial to choose the proper oil phase, which requires substantial research taking into account variables includes the nanoemulsion's stability, permeability, and viscosity. The therapeutic qualities of certain natural oils might also have an impact on the choice of oil phase.[13] The origin of the oil is crucial; for example, long-chain fatty acid-rich vegetable oils have poor emulsification capabilities and produce unstable nanoemulsions. On the other hand, oils with decreased hydrophobicity have shown improved emulsification abilities. The solubility of lipophilic medicines may be impacted by increasing hydrophobicity, however. As a result, choosing the right oil is a crucial part of developing a formulation. Oleic acid, an omega-nine fatty acid that is biocompatible and biodegradable and can be obtained in a variety of the oil phase of nanoemulgels is frequently derived from plant and animal sources. In addition to its high levels of solubilization, it is recommended for its well-documented ability to enhance percutaneous absorption and stabilise formulations.[14] Oleic acid also has anti-oxidants that help maintain the integrity of cell membranes and promote tissue and cell healing. Due to these beneficial characteristics, it is a useful permeation enhancer for many different medications, such as in the creation of topical nanoemulgels containing piroxicam.[15]

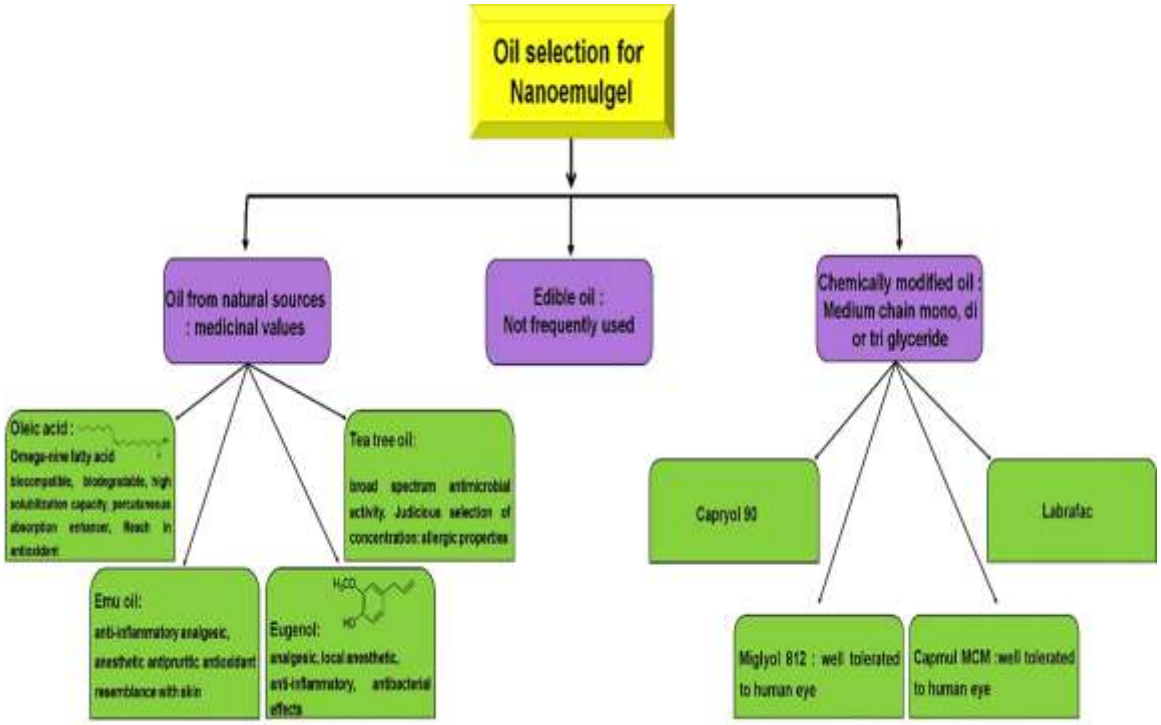

Fig 2. Choosing the oil phase during the creation of the nanoemulgel formulation.

Scientists throughout the globe are becoming more interested in natural oils for their additional therapeutic advantages in addition to their known medical capabilities. Due to its inflammatory-blocking, analgesic, numbing, anti-pruritic, and antioxidant properties, emu oil, which is obtained from emu birds, has established itself in the pharmaceutical sector.[16] These qualities have been used to produce curcumin nanoemulgels especially for the treatment of joint synovium, with enhanced permeability. owing to the abundance of unsaturated fatty acids, particularly oleic acid, emu oil has advantages that go beyond medicine. It is now being recognised in the beauty sector for its ability to moisturise skin. Drug penetration through the skin is further facilitated by this property.[17]

Tea tree oil is a well-known natural oil for its potent antibacterial properties. Tea tree oil may be helpful for treating bacterial and fungal infections when used as a component in formulations. Itraconazole, an azole antifungal drug, and tea tree oil have been combined as a stable and thermosensitive nanoemulgel that has shown a synergistic impact against vaginal

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candidiasis.[18] Using an organic solvent, improved drug loading in tea tree oil was made possible during the creation of the nanoemulgel formulation. Because of the presence of nanoscale droplets of terpinen-4-ol, the main constituent of tea tree oil, this combination improves skin penetration.[19]

Tea tree oil has a number of advantages, but its usage in formulations for transdermal distribution is restricted since it may cause allergic responses. Further analysis has shown that 1,8-cineole, a component of tea tree oil, may irritate skin. However, topical preparations with doses up to 25% have been approved as safe.[20] Consequently, when using tea tree oil as a component, careful consideration of the concentration becomes essential. Low concentrations of tea tree oil in nanoemulgels prevented irritation potential and aberrant histological results.[21]

Other natural oils have analgesic, local anesthetic, anti-inflammatory, and antibacterial properties, such as eugenol, a phenolic compound obtained from Eugenia aromatica. In ketoprofen nanoemulsion formulations, eugenol has been employed as the oil phase, resulting in a synergistic antibacterial action against Staphylococcus aureus and Escherichia coli.[22] Both the nanodelivery of ketoprofen and the inclusion of eugenol in the formulation are responsible for this. On occasion, the oil step in the creation of a nanoemulgel is the active component itself. When used as the oil phase in nanoemulgels, swieteniamacrophylla, for instance, has stronger anti-inflammatory capabilities than the plant's parent form.[23]

The best triglycerides to use for encapsulating medicines with log-P values between 2 and 4 are medium-chain triglycerides. Another medium-chain triglyceride used as the fat phase in the creation of nanoemulsions is labrafac. LabrafacTM Lipophile WL1349 was chosen from the selection to make a nanoemulgel for the transungual administration of ketoprofen. Capmul MCM is a well-known medium-chain triglyceride that is often utilised in medicinal studies.[25] It has strong water solubility and a hydrophilic-lipophilic balancing value of 5 to 6. Due to its non-irritating qualities when in touch with the human eye, it has been shown to be a good oil phase for ocular nanoemulsion compositions.[26]

Because it is well tolerated by the human eye, a particular medium-chain triglyceride called Miglyol 812 is favoured for ocular distribution by nanoemulgel formulations. The usage of this material is somewhat constrained despite the fact that it is non-irritating for ocular distribution and has a smaller nanoemulsifying area in the pseudoternary phase diagram, probably as a result of its greater molecular volume and shorter alkyl chain. However, a stable nanoformulation may be produced by careful blending and composition with the right surfactant to improve the solubility of medications with low water solubility. In a noteworthy work, Tayel et al. created a non-irritating ocular nanoemulgel of terbinafine hydrochloride utilising Miglyol 812. This formulation had enhanced bioavailability and was thermodynamically stable for prolonged release.[27]

Surfactant and Cosurfactant Selection

Surfactant

In nanoemulsion systems, surfactants are crucial for stabilising the thermodynamically erratic combination of two immiscible liquids by lowering their interfacial tension and changing the dispersion entropy. When adding surfactants into the production of nanoemulsions, a number of crucial parameters must be taken into consideration, including safety, stability, high drug loading capacity, and effective emulsification properties.[28] It is essential to choose the right surfactant. The interfacial tension should be significantly reduced as a result of its rapid adsorption at the interface between the two immiscible phases, and it should also hinder the coalescence of nanodroplets. These stabilising systems can be divided into cationic, anionic, zwitterionic, and nonionic surfactants depending on their ionic nature. Cationic surfactants include amines and quaternary ammonium compounds, anionic surfactants include carboxylate groups, zwitterionic surfactants include phospholipids, and nonionic surfactants include Capryol 90, Labrafil CS, Labrasol, Gelucire 44/14, 50 These surfactants function by generating a repulsive force between nanodroplets at the interface of the dispersed and continuous phases owing to the comparable ionic charge on the surfactant molecule's head, preventing droplet aggregation and guaranteeing the thermodynamic stability of the nanoemulsion.[29]

The choice of surfactants is influenced by a number of variables. The toxicity of the surfactant is the most important factor. It is crucial to choose surfactants that, whether applied topically or ingested, do not irritate the skin or create gastrointestinal discomfort. As a result, it is recommended to use a minimum quantity of surfactant in the formulation. Another factor is the surfactant's Hydrophilic-Lipophilic Balance (HLB)

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value, which categorises them as either oil-in-water (o/w) emulsifying agents (HLB 8-16) or water-in-oil (w/o) emulsifying agents (HLB 3-8). The chosen surfactant should have an HLB value more than 10, and surfactants like Tweens and Spans with HLB values higher than 8 are desired in order to create an o/w nanoemulsion.[30] It has been discovered that utilising Span 20 and Tween 20 together improves emulsion stability more than using each of them alone. On the other hand, surfactants with HLB values lower than 8 are used to stabilise without the use of emulsions. It is possible to create stable nanoemulsions by properly combining low and high HLB surfactants. Using mixtures of surfactants with different HLB values, researchers have successfully created stable nanoemulsions, improving stability and lowering the energy needed for formulation.[31]

Surfactant type and nature are significant selection factors as well. Due to their biocompatibility, resilience to pH fluctuations, and ionic strength, nonionic surfactants are often favoured. Ionic surfactants, on the other hand, are less preferred due to their possible toxicity. Another important aspect determining the choice of a surfactant is the surfactant's ability to solubilize oil. For instance, surfactants with the capacity to solubilize Indomethacin, such as Tween 20 and propylene glycol, were used. Similar to this, additional research found acceptable surfactants based on their solubilization properties for certain oil phases.[32] Due to their decreased toxicity, biocompatibility, compatibility with the environment, and biodegradability, natural surfactants generated from animal sources and microbial cells (including bacteria, certain yeast strains, and fungus) have attracted a lot of study attention. These biosurfactants are thought to be a possible substitute in certain industrial applications because they perform similarly to synthetic surfactants by lowering interfacial tension through amphiphilic characteristics. Rhamnolipids, for instance, have been employed successfully as natural surfactants in nanoemulsion formulations, perhaps taking the place of synthetic surfactants in certain applications. Alkyl-O-glucoside and -cellobioside biosurfactants have also been used to produce stable and low-viscosity o/w emulsions of heavy crude oil, in addition to extracts high in saponin from Brazilian ginseng roots.[33]

Cosurfactant

By helping the surfactant emulsify the oil into the aqueous phase, the cosurfactant plays a crucial part in the nanoemulsion system. In these situations, the cosurfactant interacts with the surfactant and penetrates the surfactant layer, causing the interfacial film to break down. Increased fluidity, decreased interfacial tension, and improved emulsification capacities are the effects of this disruption. Surfactants by themselves often cannot produce a fluid interfacial film or transiently negative interfacial tension. The interfacial coating is thereby made more flexible by the addition of a cosurfactant.[34]

By altering the curvature of the oil-water contact, cosurfactants may also speed up the solubilization of the oil phase. The choice of a cosurfactant is crucial because it may change how therapeutic agents or medications that are lipophilic are released by affecting how they are divided between the aqueous and oil phases via interactions with the surfactant. The cosurfactants Transcutol® HP, 1,2-propylene glycol, PEG-400, carbitol, absolute ethyl alcohol, propanol, and butanol are often utilised in nanoemulgel and nanoemulsion systems. Alcohols are commonly used as cosurfactants because their partitioning between aqueous and oil phases improves the miscibility of the two phases. Common cosurfactants include ethanol, isopropyl alcohol, 1-butanol, and propylene glycol. PEG 400 and carbitol are also often used because of their enhanced penetration and somewhat high tolerance.[35]

In nanoemulsion formulation, the choice of surfactant and cosurfactant is often made based on their % transmittance. An key factor in choosing them might be the transmittance percentage. For instance, in one research, several cosurfactants (Transcutol P, propylene glycol, and ethanol) and surfactants (Tween 80, Labrasol, and Labrafac) were evaluated based on transmittance values, with Transcutol P showing the maximum transmittance and being chosen for future formulation development.[36] The effectiveness of the surfactant in the emulsification process is significantly influenced by the concentration of the cosurfactant. The emulsion area in the phase diagram may have an impact on the choice of cosurfactant, with a longer carbon chain resulting in a bigger nanoemulsion area. Another critical element impacting the phase diagram's characteristics, particularly the size and location of the nanoemulsion area, is the mass ratio of surfactant to cosurfactant. According to studies, a 2:1 ratio of surfactant to cosurfactant produces the best nanoemulsion since it results in a bigger surface area.[37] A larger ratio of surfactant to cosurfactant

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may diminish the nanoemulsion area, while a lower ratio may not significantly reduce interfacial tension. The nanoemulsion region in the phase diagram is inversely correlated with the cosurfactant concentration, and an increase in cosurfactant concentration might result in a reduction in the nanoemulsion area.[38]

Choosing the proper components for a nanoemulsion is a challenging and important element of research, to sum up. In the section that follows, we'll look into several lab-based formulation techniques for making nanoemulsions and examine how various hydrogels may be used to alter the physical characteristics of the created nanoemulsion.[39]

Preparation of Nanoemulsion

Nanoemulgels are made in two processes, the first of which involves producing nanoemulsion and the second of which involves incorporating nanoemulsion into the gelling agent (Fig. 3).[40]

By introducing external energy to the heterogeneous mixture or by combining the compositions by reducing the interfacial tension at the oil/water interfaces, nanoemulsions may be produced.109,110 Consequently, using both high- and low-energy emulsification methods, a thermodynamically stable nanoemulsion may be created.[41]

Step 1

High Energy Emulsification Method

The oil phase is disrupted to create nanoscale droplets within the aqueous phase using high shear force generated by ultrasonicators, high-pressure homogenizers, microfluidizers, and similar equipment. The necessary parameters such as time, temperature, and properties of the components are fine-tuned to minimize the size of the dispersed phase down to the nanoscale range.[42]

As a result, the created formulations are thermodynamically unstable because they include free energy since this process of making nanoemulsions needs input from outside energy.72,113 Additionally, the size of the dispersed phase may be reduced to as little as 1 nm using this approach, while thermolabile components are ineligible for use.[43]

Low Energy Emulsification Method

In terms of the thermodynamic stability of the final formulation, the spontaneous method and the phase inversion approach are two low-energy emulsification strategies that excel above high-energy emulsification methods. Without using a lot of energy throughout the whole manufacturing process, this stability is accomplished. Oil, water, and surfactant are mixed in certain ratios to spontaneously form a nanoemulsion. Alternately, the necessary nanostructured droplets may be created and disseminated within the continuous phase by adding the aqueous phase into the oil phase while combining the surfactant with one of the media. The pH of the medium, the characteristics of the integrated surfactant and cosurfactant, and the sequence in which the components are added all have an impact on how well the emulsification process works.[44]

With regard to nonionic surfactants, namely polyethoxylated surfactants like Tween 80, Tween 60, Tween 20, Cremophor EL, Labrasol, etc., the temperature-dependent variations in hydrophilic-lipophilic balance (HLB) are specifically exploited in this approach. The thermolabile components may be added to the nanoemulsion using the spontaneous technique in particular. The temperature-dependent spontaneous change of nonionic surfactants during a phase transition is used by the phase inversion technique in contrast. By chilling the emulsion while stirring continuously, the emulsion that was created at the phase inversion temperature may be reversed. The incorporation of thermolabile components into this approach is also somewhat constrained, however this restriction may be circumvented by using appropriate surfactants that allow for a lower phase inversion temperature.[45]

Step 2

By adding gelling agents, nanoemulgel formulations may be created from nanoemulsions made using any of the aforementioned techniques. Gelling agents are primarily used in nanoemulsion formulations to change the physical state of the mixture, turning it from a liquid to a gel-like consistency. An oil-in-water (o/w) nanoemulsion solution is thickened by the addition of by encouraging the formation of a gel-like structure, a gelling agent. The ability of the gelling agent to transition the formulation from a gel to a solution when subjected to shear stress without affecting its volume allows for this transformation. Additionally, the condition automatically switches from a solution back to a gel as you stand up.[46]

In order to completely accomplish swelling, the gelling agents must be dissolved in an aqueous medium while being continuously stirred at a steady pace for a certain amount of time to

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generate the gelling medium. The produced gel is then filled with the emulsion at a precise ratio while being continuously mixed to maintain homogeneity. In the portion of this article that follows, the effect of nanoemulgel formation on the pharmacokinetic and pharmacodynamic characteristics of the medication is further examined.[47]

Formulation of nanoemulgel and it's impact

The pharmacokinetic characteristics of a medicine may be considerably altered by adding a hydrogel matrix to a nanoemulsion. Lipophilic medicines are often included into the lipid phase prior to the creation of the nanoemulsion. The appropriate medication inclusion depends on the lipid phase being chosen. The degree of the medicinal component's entrapment in the nanoemulsion is often assessed using sophisticated analytical methods like HPLC.[48]

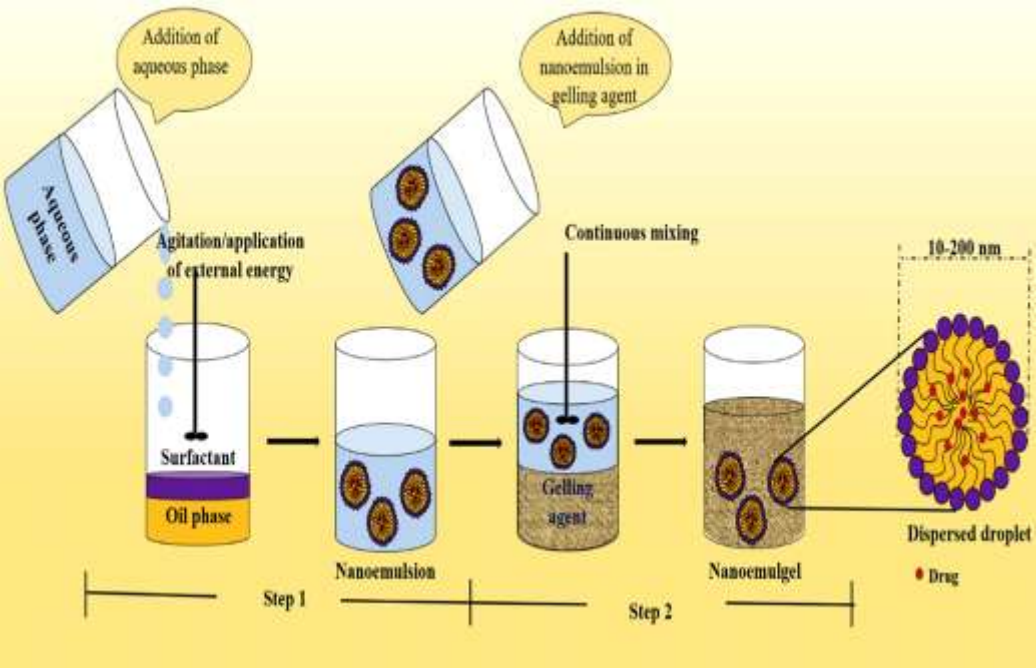

Fig 3 Preparation of Nanoemulgel

For instance, the invention and improvement of lornoxicam nanoemulgel were the topic of a recent research by Dasgupta et al. However, a unique strategy was used in this case. The researchers dispersed the chosen oil, Labrafac, into the gelling agent's dispersed phase as opposed to adding the optimised nanoemulsion directly (as previously reported, using 1% wt/wt Carbopol 934). The gel was then neutralised by the addition of triethanolamine. The selected cosurfactant (Pluronic F68) and surfactant (Tween 80) were then gradually mixed into the gel, resulting in the development of a nanoemulgel by the addition of the remaining aqueous phase. After neutralising the generated nanoemulgel with 0.5% weight/weight triethanolamine, it was discovered that its pH was in the range of 6-7. It was said that cutaneous application is good for a neutral pH.[49]

When compared to a commercial gel formulation, in vitro tests showed that both nanoemulsion and nanoemulgel considerably increased skin release and penetration flux. The nanoemulsion formulation has the strongest in vitro release and permeation flux of lornoxicam. A longer drug release behaviour in the nanoemulgel is one possible effect of the decreased flow in the nanoemulgel compared to the nanoemulsion. Following that, pharmacodynamic tests showed that both nanoemulsion and nanoemulgel worked better than the commercial product in reducing paw edoema in male Wistar rats using the Complete Freund's Adjuvant-induced paw edoema paradigm.[50]

Another research carried out by Khurana et al. revealed the increased skin penetration and sustained release features of a meloxicam carrier gel. In addition, the new formulation showed considerable anti-inflammatory action while being nonirritating, hemocompatible, and nontoxic. Nanoemulgel was also shown by Pund et al. as a

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promising carrier for the treatment of psoriatic arthritis and skin with melanoma. Ex vivo permeability of the medication via rat skin was effectively increased by the research team to approximate transdermal permeability of the formulation. Additionally, it was discovered that the new formulation caused cell-specific cytotoxicity against human melanoma cell lines, supporting the formulation's safety towards normal cells.[51] It was suggested that this formulation's transdermal distribution might target site-specific therapy, perhaps lowering the necessary medication dosage and decreasing systemic side effects. After 12 hours of exposure to the nanoemulsion, Rat skin histopathological sections showed no alterations to the skin architecture. The aryl hydrocarbon receptors were upregulated and had an antiproliferative effect in the test cell lines, according to in vitro research on the A375 and SK-MEL-2 cell lines.[52]

Additionally, a comparable strategy for mycological treatment using nystatin nanoemulgel produced the maximum drug release in comparison to solid dispersion or commercial cream formulations. The creation of a nanoemulsion of the antihypertensive drug telmisartan was significant for the utilisation of carbopol 934. This research showed a considerable increase in drug permeability and a correlation between ex vivo skin permeation results and in vivo findings.[53] This rise may be attributable to the drug's surface area, which has significantly increased in the nanoemulsion, improving its solubility and ability to pass through lipidic tissue barriers. In a different work, Elosaily et al. described creating a nystatin nanoemulsion using a spontaneous emulsification process. They then added this to a viscous solution of 5% methyl cellulose to create a nanoemulgel. When the medication's solid dispersion gel and specially made nanoemulgel were compared, it became clear that the nanoemulgel released the drug at a greater rate.[54]

Sampathi et al. conducted a noteworthy work in which they created an itraconazole nanoemulgel formulation. Lecithin and sodium cholate were used as surfactants, and the researchers first produced the nanoemulsion by ultrasonication after heating the medication in eugenol to dissolve it. The pH was subsequently adjusted using triethylamine and Carbopol 934 to transform the optimised nanoemulsion into a nanoemulgel. In order to improve penetration and serve as an odour masking agent, this formulation included 0.1% limonene. Itraconazole hydrogel based on nanoemulsions outperformed drug solution in terms of penetration and in vitro release. The formulation showed a prolonged release profile, which might lower the number of doses needed.[55]

Similar to this, Tween 20, Labrasol, and Carbopol 934 were used as the proper surfactant, cosurfactant, and gelling agent when Mirza et al. constructed an itraconazole and tea tree oil nanoemulgel formulation. The results showed that, while having a same amount of polymer, the nanoemulgel formulation had a greater flux and better drug permeability than traditional gel. In a separate situation, Eid et al. produced a nanoemulsion formulation of Swietenia macrophylla oil using carbopol 940 as a gelling agent, evaluated its therapeutic effectiveness, and subsequently produced a nanoemulgel. Compared to Swietenia macrophylla oil solution, Swietenia macrophylla oil nanoemulgel significantly reduced inflammation in carrageenan-induced rat paw edoema.[56] Arora et al. embarked on the formulation of a groundbreaking nanoemulsion featuring ketoprofen via a low-energy method. Carbomer 940 was utilized to transform this nanoemulsion into a nanoemulgel. Excipient selection was based on a comprehensive evaluation that considered solubility, transmittance, drug content, spreadability, rheological characteristics, ex vivo drug penetration, and resilience under pressure all affect thermodynamic stability.[57]

Additionally, a research concentrating on stratifin and acetylsalicylic acid-loaded nanoemulgels found a sustained drug release profile that markedly enhanced rabbit ear wound healing with daily dressing. Fewer applications of this formulation were required, and it proved more effective in reducing epidermal hypertrophy compared to the carboxymethyl-cellulose gel. Moreover, it led to a substantial decrease in tissue cellularity and collagen density. Yang et al. used chitosan and the cationic polymer polylysine to create a diclofenac sodium microemulgel utilising a low-energy technique. When compared to the commercial emulgel and hydrogel formulations of the same medicine, the skin penetration rate of the drug from the optimised formulation was 1.86 to 5.76 times higher. Remarkably, the microemulgel demonstrated self-preserving activity when polylysine was incorporated into the formulation.[58]

In addition to transdermal usage, nanoemulgels are currently being used to treat periodontitis, ocular delivery, cosmetic problems, vaginal infections, and other conditions. As an

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example, Srivastava et al. created a nanoemulgel for the nonsteroidal anti-inflammatory drug ketoprofen to treat periodontal disease. Eugenol was used in the formulation as the oil phase, while Carbopol 934P and Poloxamer 407 were used as gelling agents. Notably, slower burst releases of the medication from the nanoemulgel were caused by greater Poloxamer 407 concentrations.[59] The ketoprofen nanoemulgel showed a substantial decrease in gingival index, tooth mobility, and alveolar bone loss in pharmacodynamic tests targeted at periodontitis. Histopathological examinations of the molar teeth showed that this was supplemented by a decrease in inflammatory cell infiltration, alveolar bone resorption, and cementum loss. Jeengar et al. recently unveiled a curcumin nanoemulsion made with emu oil to treat arthritic conditions. This curcumin-loaded nanoemulsion successfully addressed the drawbacks of low solubility and poor penetration of curcumin by being added to a carbopol gel. Application of both low- and high-dose curcumin nanoemulsion-loaded gel dramatically decreased bone damage in an experimental model of adjuvant-induced arthritis. Radiological scoring showed reduced bone damage, and the inhibition of cartilage damage, synovial space damage, and cellular infiltration in the synovial cavity was evident. Histopathological data further confirmed the improvement in arthritic conditions.[60]

The application of nanotechnology through nanoemulgel techniques extends beyond transdermal delivery. It has sparked interest in fields such as periodontitis, ocular treatments, cosmetology, vaginal infections, dental care, and more, promising enhanced drug delivery efficiency and effectiveness.[61]

II. CONCLUSION

Since there are several components that make up nanoemulgels and each one has unique qualities, choosing the right ones and figuring out their best concentrations call for knowledge. Surfactants, cosurfactants, oils, and gelling agents are some of these ingredients. Additionally, the choice of manufacturing methods is crucial since it has a big impact on the features of the finished formulation. Consequently, the basic process and the careful selection of components are what will determine whether a transition from nanoemulsion to nanoemulgel will be thermodynamically stable.

For transdermal distribution, the creation of hydrogel-thickened nanoemulgels from standard nanoemulsions has found to be more effective and compatible. By lowering interfacial tension and restricting the mobility of the dispersed phase, the viscosity of this formulation increases its thermodynamic stability. As a result, it provides an effective and enhanced topical administration mechanism for pharmaceuticals, especially for lipophilic drug compounds. This promotes improved contact time, the development of a thin layer over the skin, and skin hydration while enhancing skin permeability into the deeper layers. These nanoemulgels' commercialised compositions hint to possible therapeutic advancements and have sparked research interest in this novel dosage form.

Hydrogel-based nanoemulsions have been successfully used in a variety of pathophysiological circumstances, which highlights the substantial advancements made by formulation scientists in the pharmaceutical sector. The non-greasy, gel-like, continuous release qualities that accompany topical administration, however, make user acceptability a focus. The creation of nanoemulgels has potential for including active ingredients to fight viral, bacterial, fungal, and even melanoma infections. However, more molecular analysis of medication absorption mechanisms is still necessary. As a consequence, this innovative transdermal dosage form offers an intriguing field of study, focusing on particular dermatological problems as well as enhancing the treatment of other systemic diseases.

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