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Microemulsion Therapy for Acne

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ABSTRACT
Common dermatological disorder acne is distinguished by its complex underlying causes. The patient's quality of life may be greatly impacted by its frequent occurrence in therapeutic practise. Numerous treatment plans call for repeated applications of topical medications over a lengthy period of time. Innovative topical carriers that may encapsulate anti-acne chemicals provide a viable alternative to the present conventional methods to meet the challenges of treating such a multifaceted skin disease. Microemulsions excel in delivering drugs, especially those with either hydrophilic or lipophilic characteristics, making them a standout in this context. This study analysed these transparent, thermodynamically stable complexes as extraordinary structures capable of penetrating the skin barrier and supporting targeted treatment for acne. They only included a small number of basic elements.

I. INTRODUCTION

Our body's main contact with the outside world is the skin, which is sometimes compared to a complex mantle. Its function in coordinating essential processes strikes a good balance with its inherent brittleness and sensitivity. From childhood to old age, these traits follow us on our life's journey. They are especially pronounced in pathological situations that need specific care from the patient and their healthcare practitioner.[1] Dermatologic conditions are widespread around the globe and have a considerable negative influence on patients' quality of life, both physically and mentally. In terms of non-fatal injuries, skin conditions were in fourth place in 2010 and 2013 according to the Global Burden of Disease Project. Genetic, underlying systemic, regional, and socioeconomic variables all have a role in the development of these disorders, which often result in lowered quality of life owing to insufficient access to healthcare.[2]

One of the top ten most frequent illnesses globally is acne, a widespread chronic skin ailment. Clinical practise commonly encounters its recurrent character, and suitable therapy suggestions always come after a thorough and certain diagnosis. In the past, dermatologists have identified skin signs via ocular examination. Acne treatments may be specifically designed utilising traditional or modern pharmaceutical formulations by identifying distinct skin patterns and comprehending the course of acne. Carefully chosen pharmaceutical formulations provide accurate and efficient therapy.[3]

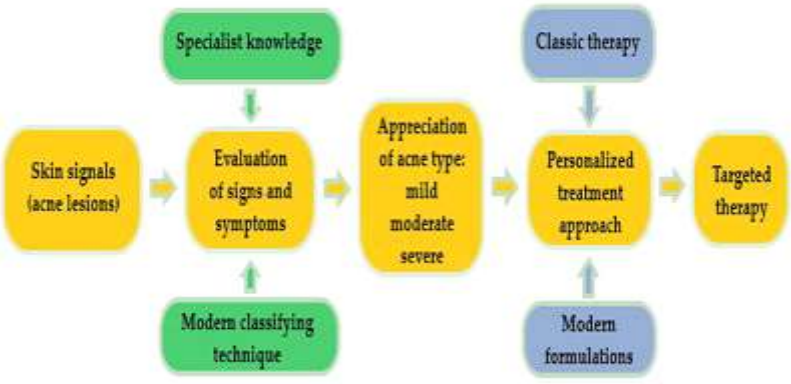

Fig 1. Diagram illustrating the need of an accurate diagnosis for individualised care in dermatologic illness.

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To get through the strong barrier created by the stratum corneum, several treatment techniques have been used to increase the bioavailability of dermatologic medicines at the skin site. A deliberate effort is also being made to study the possibility of integrating systemic medications into topical formulations rather than only administering them orally.[4]

Nanotechnology is essential to this project because it helps create novel formulations with better medicinal results. Microemulsions have become well-known in the study of nanocolloids as flexible systems capable of addressing a variety of drug delivery challenges. They have the benefit of being easy to prepare since they only need a few components, specifically, water, a cosurfactant, a surfactant, and oil. adding lipophilic or hydrophilic actives that can dissolve within a phase is also possible with the help of microemulsions. Microemulsions are positioned as a viable owing to the creation of stable, transparent As a base for creating nanoparticles, dispersions containing tiny particles may pass through biological membranes.5 Additionally, microemulsions are acceptable when they include biocompatible oil sources, such as vegetable oils, natural surfactants, or biopolymers as ecologically friendly medications. that are appropriate for topical or systemic therapeutic administrations with focused effects.[6]

The creation of oral microemulsionate systems that better absorb drugs by employing medium-chain fatty acids and their salts as carriers like calcein was the focus of early research in the 1990s. Extensive solubilization tests were carried out on substances like testosterone propionate to determine the ideal oil phase. It has been shown that oil-based solubilizing agents are crucial in the manufacture of microemulsions, significantly influencing their internal behaviour and requiring careful inspection and selection during formulation.[7]

Numerous biological applications were investigated, proving the efficiency of delivering microemulsions within the human body. In recent achievements, we have witnessed significant milestones in the area of medication distribution. These include the injection of zidovudine via the nose, the sublingual administration of insulin, the use of fusidic acid to treat wounds, the vaginal administration of fluconazole, and novel transdermal drug delivery techniques., and the development of self-microemulsifying systems capable of generating microemulsions in biological fluids for oral delivery.[8] These breakthroughs have resulted in substantial improvements in the solubility and bioavailability of various molecules utilized in the topical treatment of dermatologic conditions. Notable examples include the enhanced delivery of cyclosporine for Psoriasis, ceramides for reshaping the skin, imiquimod for actinic keratosis or basal cell carcinoma, penciclovir, acyclovir, and tenoxicam for the treatment of rheumatoid arthritis.[9]

A New Vision for an Optimum Acne Therapy Utilises Microemulsions

Active anti-acne compounds are used in contemporary formulations, which provide interesting options that need further examination in order to be possibly incorporated into clinical practise for dermatologic treatment. Vesicular nanosystems, which include a variety of lipid-based structures including one prominent subcategory of these formulations. Furthermore, systems based on hydrogels have shown greater results and the ability to include nanoparticles.[10]

Liposomal formulations are characterised by spherical vesicles that have a hydrophilic core and a dual lipophilic membrane made of cholesterol and phospholipids. This gives birth to the spherical shape of the formulations. The structural differences of the other aforementioned vesicular systems. A noteworthy benefit that has prompted the creation of several anti-acne formulations is the capacity to encapsulate hydrophilic or lipophilic chemicals. Positive outcomes have been seen with respect to the solubilization, protection, and release of active pharmaceutical ingredients (APIs) in vesicular systems containing clindamycin, dapsone, azelaic acid, erythromycin, salicylic acid, or rhodomyronine as well as liposomal formulations containing tretinoin or adapalene.[11]

Vesicular formulations are widely used in medicinal applications, however they do have certain drawbacks. Due to their size, which ranges from 50 nm to 500 nm, they are vulnerable to oxidative and hydrolytic processes. The scale of aggregate phenomena may alter unexpectedly, and the preparatory processes may be time-consuming and expensive.[12]

Given these factors, the scientific literature emphasises the value of microemulsions as a potential class of delivery systems for anti-acne substances, with positive results shown throughout the assessment process.[13] Microemulsions and nanoemulsions stand out as contemporary colloidal dispersions having multiple

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benefits, including enhanced bioavailability of active ingredients, thanks to their extensive research and wide range of pharmaceutical uses. Both methods resemble conventional emulsions in certain ways, but they also use a co-solvent, often known as a cosurfactant, to produce special vehicles that get around the difficulties of incorporating APIs into topical formulations.[14]

Particle size is a key factor in distinguishing micro- and nanoemulsions, with microemulsions commonly having particles between 10 and 100 nm and nanoemulsions having particles up to 200 nm. Thermodynamic stability and preparation techniques are other differences. In contrast to nanoemulsions, which must be prepared using high-pressure homogenizers or certain sonication techniques because they are thermodynamically unstable but kinetically stable, microemulsions may develop spontaneously.[15] It is clear that microemulsions provide tailored properties in light of these subtle variations within the field of nanosystems. Their use in dermatologic treatment has the potential to open up new channels for the administration of specialised drugs, having a favourable impact on the treatment of skin disorders like acne.[16]

General Concept

This ground-breaking accomplishment served as the catalyst for the development of what are now known as microemulsions, or smart colloidal systems. In the beginning, their main usage was concentrated on creating chemical-based methods for industrial oil recovery procedures. Since then, new ideas have been revealed and our knowledge of physical phenomena, their intricate structural makeup, and their processes of action has grown, especially in the fields of medicine and pharmaceuticals.[17]

Consideration should be given to three important characteristics, including component type, particle size, and thermodynamic stability, to distinguish microemulsions from conventional emulsions. Coarse dispersions called emulsions are created when two immiscible phases are kept together by an emulsifier. The external phase, also known as the continuous phase or dispersion medium, disperses the internal phase, also known as the discontinuous phase. Emulsions generally have particle sizes between 1 to 100 m, Consequently, they are opaque systems with high interfacial energy.[18] However, the stability of the dispersed particles within the continuous phase is ensured by the low values of their interfacial tension. Emulsion systems have been used in current applications for a very long time., especially in the form of fluid or semi-solid vehicles in dermatologic and cosmetic treatments. However, thermodynamic instability, which causes problems like flocculation, coalescence, creaming, sedimentation, and Ostwald ripening, is to blame for their little useful life. Additionally, complicated formulation issues for active compounds make emulsion formulations inappropriate.[19]

Microemulsions (MEs), on the other hand, are described as microheterogeneous dispersions distinguished by their extraordinary thermodynamic stability. The monophasic and isotropic architectures of these systems, which generally consist of an oil phase and an aqueous phase stabilised by a combination of surfactant (S) and cosurfactant (CoS), give them their translucent appearance. Physical markers of their size, which commonly falls between 5 and 100 nm, include their clarity and uniformity.[20] Depending on whether oil particles are distributed in an Microemulsions may be categorised as either oil-in-water (O/W) or water-in-oil (W/O) if there is an aqueous phase or water droplets are dispersed in an oil phase., with stability being provided by the appropriate S/CoS combination. A special kind of microemulsion known as a bicontinuous microemulsion is one that needs the same quantities of water and oil in the system to form at the phase inversion temperature. Pseudoternary phase diagrams and the Winsor phase notion are used to describe practical features, such as changes in ME types and their behaviour. A crucial topic of research in the discipline of ME thermodynamics is the examination of the internal structure of microemulsions.[21]

At the beginning of the formulation process, the benefits of microemulsions are an important factor that is directly related to the active ingredients to be included. The finished product has a simple composition but a complicated structure. An overview of the benefits that make microemulsions the best option for the topical distribution of active ingredients.[22]

Physicochemical Concepts

A crucial aspect of microemulsions that has drawn a lot of Their thermodynamic stability is of importance in their investigations. Five separate theories have been created to better describe the behaviour of microemulsions, directing research from basic ideas to contemporary findings. Thermodynamic theory, interfacial film theory,

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Bicontinuous microemulsion theory, solubilization theory, and micellar state theory are all included in this group. Initial understandings of the structure and stability of microemulsions are provided by each of these theoretical frameworks, which may then be furthered by solitary discoveries within certain system categories.[23]

The first theory, known as the thermodynamic theory, uses the equation of free energy as a fundamental analytical framework to explain the thermodynamic processes that take place inside microemulsion systems.[24]

Gf=y.a-T.S

The interfacial tension (), typically characterized by its low values, is manifested in the dispersion medium, on the top of submerged particles (a). This tension plays a pivotal role in determining the system's energy and is influenced by factors such as an increase in entropy (S) and temperature (T).[25] The system is more stable when the particles have a bigger surface area. A cosurfactant may also be added According to the hypothesis of interfacial film formation, encourage zero or even negative levels of interfacial tension. With the aid of these discoveries, a three-step explanation of how an interfacial monolayer forms and promotes stability in microemulsions may be provided.[26]

1. The creation of a monomolecular film results from the surfactant's crucial function in lowering the Interfacial tension at the water-oil interface phases in a system that contains both water and oil.[27]
2. The initial interfacial tension is further reduced by the addition of a cosurfactant. Alongside the surfactant particles, the cosurfactant is largely concentrated near the interface.
3. This system has a free energy that makes it easier for microemulsion droplets to develop that are 1-100 nm in size while remaining macroscopically undetectable. Their detection requires the use of precise experimental methods, such as transmission electron microscopy (TEM). These techniques reveal certain particle assemblages.[27] For instance, in a research by Reis et al., babassu oil, representing 12.2% of the active oil component renowned for its anti-inflammatory qualities, was formed into oil-in-water (O/W) microemulsion systems. This was spread out across a 39% water medium in the system. The interior structure was revealed by TEM imaging, which also disclosed information on the sort of microemulsion and the architecture of the particles. Notably, this visualisation demonstrated the existence of droplets in the babassu oil phase.[28]

The surfactant-surfactant monolayer-sheathed microemulsion droplets are incorporated into the aqueous medium. Furthermore, the formulation included a surfactant (S)/cosurfactant (CoS) mix that included Cremophor EL at 9–27% and Transcutol at 8–27%. The existence of spherical oil phase particles that are successfully stabilised within the aqueous medium and each measure under 100 nm in dimension was discovered by TEM investigation. A helpful technique for examining material structures is confocal laser microscopy, which is commonly used in the characterisation of microemulsions.[29-30]

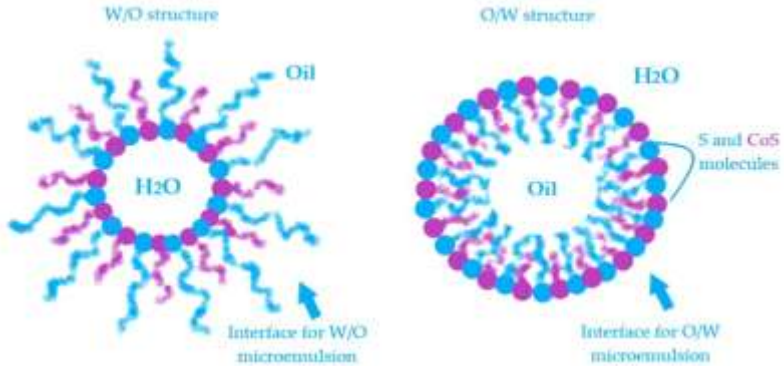

Fig 2. Exemplification of the model structure

The framework of the theory of elastic masses may be used to understand the stability of microemulsions. According to this viewpoint, microemulsion droplets are perfect spheres suspended in a continuous phase, where two primary characteristics, elasticity, and rigidity against particle distortions, play a crucial role. The concept of elastic particles contributes to research regarding particle size, offering insights into mean

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particle dimensions, the polydispersity index, interfacial tension, and solubilization capacity.[31]

Particularly, three elasticity constants apply to microemulsion particles. The first one affects the phase type and improves stability. It is called spontaneous curvature. Better solubilization ability and a bigger number of particles stabilised with more surfactant content are related to a lower spontaneous curvature value. The stiffness constant, which maintains the surfactant's resilience to unwelcome curvature changes, is the second factor. The stiffness constant rises as the third constant, the deformation (saddle-splay) constant, decreases, which promotes system stability.[32]

The formation of micelles is emphasised as a characteristic shared by micelles and microemulsions in the notion of the micellar state. A surface tension modulator (S) is selected in both scenarios. Microemulsions, on the other hand, set themselves apart by include a cosurfactant, producing intricate structures.[33] Taylor dispersion analysis is a useful technique for differentiating between micellar structures and microemulsions. With this technique, materials are introduced into a capillary, and over time, the hydrodynamic radius of the particles is measured. For instance, this technique was utilised to analyse, offering important insights regarding system stability.[34]

The solubilization hypothesis, which leverages the pre-Ouzo phenomena, offers fresh insights on the spontaneous microemulsion creation without surfactants in addition to the conventional composition of microemulsions.[35] We use a model system with water, n-octanol. Similar to this, ethanol may be used as a co-solvent to create ternary microemulsions with water and eugenol. As a quick substitute for sonication techniques, the addition of ethanol as a co-solvent has a hydrotropic effect that turns by means of spontaneous emulsification, a turbid system may become clear.[36]

The fourth and final hypothesis focuses the microemulsions' four Winsor stages and deals with bicontinuous microemulsions. According to this theory, a microemulsion with a continuous hydrophilic phase can change into a system with a continuous lipophilic domain when the oil phase is added gradually.[37] This transition occurs after a bicontinuous intermediate state in which the hydrophilic and lipophilic domains coexist in a chaotic but stabilised way thanks to surfactants. In a research by Kogan et al., this behaviour was seen for microemulsions made of triacetin, D-tocopherol acetate, ethanol, and Tween 60. By dilution with the aqueous phase, the system was converted from a water-in-oil (W/O) microemulsion to an oil-in-water (O/W) microemulsion, showing the significance of Winsor phases in directing the formulation and manufacture of microemulsions.[38]

The Winsor phases present in microemulsion formulations are shown in Figure 3 as follows: Oil-in-water (O/W) microemulsions in equilibrium with an excess of the oil phase in the top section of the vial are what are referred to as Winsor phase I. Water-in-oil (W/O) microemulsions with an excess of the water phase in the bottom section of the vial are represented by Winsor phase II. Winsor phase III describes a ternary mixture at equilibrium with an excess of the aqueous phase in the lower zone, an excess of the oil phase in the upper zone, and a microemulsion in the intermediate area. A monophasic domain without phase excess is another feature of the ideal Winsor IV system.[39]

Fig 3. Winsor phases I, II, III, and IV are shown schematically to show how the phases change from Winsor phase I to Winsor phase IV to produce an ideal system.

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Formulation of Microemulsions

In the formulation of microemulsions, the primary focus is on creating a well-balanced mixture of surfactant (S), cosurfactant (CoS), and the oil phase, often with the addition of an appropriate amount of aqueous phase, typically distilled water.[40]

A molecule having specific capabilities for modifying surface tension inside the system in which it is used is referred to as a surfactant, also known as an emulsifier. This molecule is made up of hydrophilic and hydrophobic structural elements, which are similar to two opposing poles that orient themselves preferentially when they interact with the system's particles, such as oil and water molecules. In the context of the interfacial film theory, the surfactant plays a pivotal role in By forming an interfacial monolayer, the dispersion process gives particles in the continuous phase the flexibility they need.[41]

An exceptional feature of microemulsions is the relatively high proportion of the surfactant/cosurfactant (S/CoS) mixture, often reaching up to 70%, in contrast to conventional emulsions, approximately 10–20% of the formulation is usually made up of the emulsifier. Following the "Generally Regarded as Safe" (GRAS) guidelines, the formulation of topical systems necessitates a comprehensive investigation of the chemicals to make sure they are non-toxic, non-irritating, and biocompatible. Natural surfactants are increasingly being used as a sustainable alternative to synthetic ones, and algorithms are often used to lower the high concentration of S/CoS mixes while retaining improved system stability.[42]

Labrasol, a derivative of polyethylene glycol (PEG) generated from medium-chain fatty acid triglycerides (C8-C10) present in capric and caprylic acids, is another option often used in the creation of microemulsions (ME). Also often used in ME formulations are Cremophor derivatives as polyoxyl 40 hydrogenated castor oil (Cremophor RH 40) and polyoxyethyleneglycerol triricinoleate 35 (Cremophor EL, Kolliphor EL).[43]

Particularly in the field of biocompatible tensioactives for drug administration, have drawn a lot of interest as good candidates for creating microemulsions. The surface activity and biodegradability of these surfactants are highly valued, making them good candidates for the creation of topical systems. As an example, Fanun has suggested a possible method for solubilizing active substances that combines the ethoxylated mono- and diglyceride combination Mazol 80 with sucrose laurate, water, and peppermint oil.

The cosurfactant (CoS), which also has the ability to serve as a co-solvent, is the mixture's second component. CoS has the ability to lower interfacial tension, which improves the flexibility of the microemulsion's particle structure. CoS molecules guarantee great solubility for both hydrophilic and hydrophobic compounds, and they are investigated as penetration enhancers, especially in skin delivery applications.[44] Medium-chain alcohols (C2-C10) are the primary CoS agents chosen for ME production. Due to their biocompatibility and extra solubilization abilities for active pharmaceutical ingredients (APIs), which may be seen during screening methods, propylene glycol and transcutol p are often used. Abd Sisak et al.'s comparative analysis showed that Transcutol P and PG were more effective than PEG 400 at generating large ME areas in systems made with Brij 97, oleic acid, and water.[45]

To ensure efficient encapsulation, the active pharmaceutical ingredient's (API) solubility must be taken into consideration while choosing the oil phase. ME formulations often choose synthetic oils such isopropyl myristate, ethyl oleate, and oleic acid. In contrast, vegetable oils, particularly those with low molecular weight and medium-chain fatty acids, have become more and more popular for use in ME preparation. Vegetable oils also provide renewal, protection, and moisture for the skin. Hortolomei et al.'s investigation on creating MEs using avocado oil and a S/CoS combination including sucrose laurate and Transcutol P was one example of this. This method put more emphasis on the formulated systems' potential for skin administration while also suggesting improved tolerability.[46]

According to a short research by Scomoroscenco et al., grape seed oil has recently been used to build ME systems. These systems combined Plurol diisostearique CG, Tween 80, and an ethanol-based S/CoS. the lipophilic phase when grape seed oil was used, the resulting cosmeceutical microemulsions worked well.[47] When Pterodon emarginatus oil was used to create microemulsions, Pascoa et al. found that the anti-inflammatory effects of the microemulsions were superior to those of the oil alone.[48]

For its antioxidant and moisturising qualities at the skin site, olive oil was added to oil-in-water (O/W) microemulsions in a research by Chaiyana et al. all had an effect on the creation of bigger microemulsion regions, which had a

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substantial influence on how well they worked on the skin. Due to its humectant qualities, propylene glycol had a favourable effect on skin hydration and shown comparability While ethanol preserved the anti-oxidant activity of olive oil, it was combined with a hyaluronic acid formulation.[49]

Essential oils (EO) are another group of oil types that are widely used in microemulsion (ME) formulation and have a significant influence on skin delivery. Through extraction procedures, essential oils are produced from a variety of fragrant plant components. The therapeutic effects of the active ingredients in essential oils on the body's biological processes are diverse. Due to their lipophilic characteristics, terpenes, a significant class of chemical molecules found in essential oils, contribute to the destabilisation of the stratum corneum. It is essential to take into account the terpene structure and their physicochemical properties while preforming MEs.[50] For lipophilic actives, non-polar terpenes with a high level of unsaturation are favoured, while species containing hydroxyl groups, characterised by a low level of unsaturation, might be chosen for hydrophilic medicines. The benefits of using essential oils and their role in the creation of anti-acne microemulsions are highlighted.[51]

Methods for Microemulsion Preparation

Microemulsions are thought of being adaptable systems that may be created with little expense or energy. The room-temperature preparation procedures rely on two titration techniques that may be modified according to the phases selected, their concentrations, and the kind of microemulsion sought. The phase titration method and the phase inversion method, using either the oil phase or the aqueous phase, are used in practise when using the microemulsification technology.[52]

The shift from an oil-in-water (O/W) type to a water-in-oil (W/O) type microemulsion happens via changes in curvature orientation, resulting in a characteristic state of bicontinuity, in accordance with the particle notions covered in the introductory theories section. Figure 4 shows how this shift is followed by structural changes.[53]

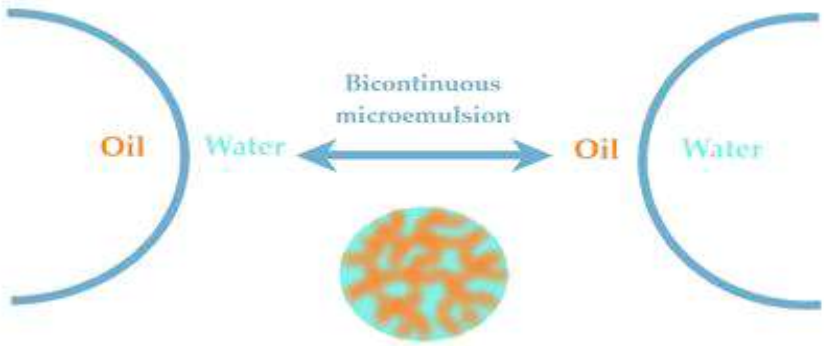

Fig 4. Schematic The phase transition from oil in water to water in oil

A pseudoternary phase diagram design may be used to determine the area of microemulsion formation based on the quantities chosen for the S/CoS mixture, oil phase, and aqueous phase. In difficult study where various combinations of tensioactives and oil phases are tested, it was found that the graphical analysis based on diagrams was an essential step to proceed with an experimental design in order to produce the best microemulsions. Pseudoternary phase diagrams, which show zones particular to O/W, W/O, and biocontinuous microemulsions, provide a useful method for analysing the stability of microemulsions in a wide range of research.[54]

Application of Microemulsions for Anti-Acne Drug Delivery

Many research projects have been devoted to developing novel formulations that provide improved control over acne pathogenesis by precisely targeting active pharmaceutical ingredients (APIs) to providing an alternative to traditional therapy modalities at the skin location.[55] The majority of these innovative techniques were

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developed to address issues related to the solubility of lipophilic actives, including vitamin E, retinoids, antibiotics, and other antimicrobials like metronidazole or dapsone. Through the avoidance of contacts and photochemical reactions, this strategy not only increases solubility but also provides protection against undesirable internal processes. The stratum corneum is easily penetrated by Acne therapy adjuncts include hydrophilic substances including vitamin C, azelaic acid, nicotinamide, and hyaluronic acid.[56]

The potential of 3% essential basil oil (extracted from Ocimum basilicum) was employed by Pansang et al. as an oil phase in the development of anti-acne microemulsions. The microemulsion's skin tolerability was tested on 30 individuals, demonstrating the vehicle's safety when used topically.[57]

Additionally, using the antibacterial qualities of orange oil, Jantrawut et al. created microemulsion systems. These microemulsions were designed to be applied to skin as a pectin film, allowing for intimate contact with tissue. The research emphasised the relevance of choosing appropriate surfactants and cosurfactants to produce wide areas of microemulsion and the fundamental elements of microemulsion design.[58]

With each of the chosen phases, it is evident that the formulation parameters significantly affect the microemulsion properties. having a crucial impact on the ultimate effect of the API at the desired location. API localisation in different skin layers is greatly improved by microemulsion systems, which may also be further optimised by using the Quality by Design principles. Tolerability and biocompatibility at the application site may be improved by using Combination systems that include excipients that are naturally sourced include gels or emulgels that are based on microemulsions.[59]

II. CONCLUSION

The development of topical remedies to support the healing process in dermatologic illnesses may greatly benefit from the research of nanocolloids. Due to their unique internal structure, microemulsions, which are a component of soft matter systems, exhibit great stability, biocompatibility, and tolerability and positively affect the dynamics of the skin. As a result, the pseudoternary structure of oil-surfactant/cosurfactant-water represents a balanced composition. may be used to overcome the constraints of traditional systems. Numerous strategies were put out to improve the skin's bioavailability of both hydrophilic and lipophilic anti-acne chemicals, providing a route to more effective topical pharmaceuticals. This leads to the conclusion that microemulsions are excellent delivery systems for anti-acne medications.

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