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A Review on Microemulsion

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Abstract:

Microemulsions are technologically important complex liquids. In many applications, they have to accommodate functional additives such as drugs, polymers, and nanoparticles, which further increase the complexity of the systems. Several complementary techniques are required to understand and manipulate the behavior of microemulsions. Microemulsions are clear, stable, isotropic mixtures of oil, water, and surfactant, often in combination with a co-surfactant. These systems are currently of interest to pharmaceutical scientists as they have significant potential to act as vehicles for drug delivery by integrating a wide range of drug molecules. To appreciate the potential of microemulsions as transport vehicles, this commentary focuses on a detailed description of the concept of microemulsions, how they can be formed, factors affecting stability, and recent applications. The use of microemulsions as drug delivery vehicles has been an exciting and attractive area of research due to their many potential and unique advantages.

Keyword- NanoParticle, Transparency, Co-Surfactant, Potential.

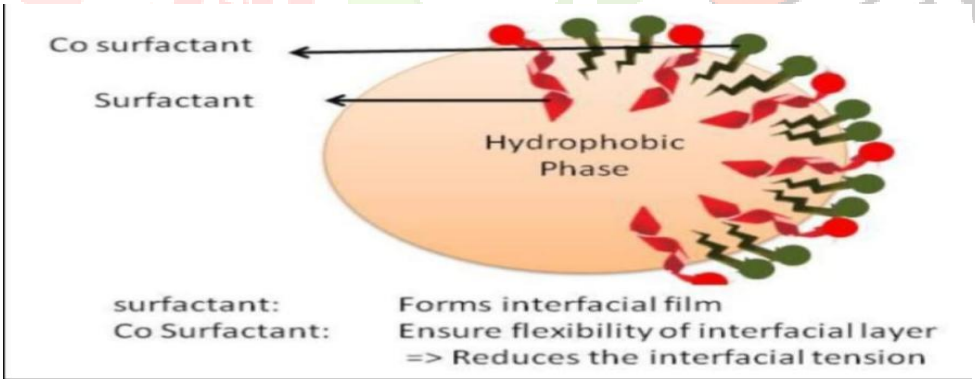
Introduction :

Microemulsions are a clear, stable, isotropic liquid mixture of oil, water and surfactant, often in combination with a surfactant. Formulating and developing a new drug delivery system with the aim of improving efficacy is an ongoing process in pharmaceutical research. Since then, many types of drug delivery system have been developed. They prepared the first microemulsion by dispersing oil in an aqueous surfactant solution, and microemulsion by adding an alcohol as a co-surfactant, resulting in a clear, stable formulation.[1]

Microemulsions have attracted considerable interest over the years as potential drug delivery systems. Formulations based on microemulsions have several properties, namely increased drug solubilization, good thermodynamic stability and ease of manufacture. Microemulsions are versatile systems and can be used to deliver drugs in a variety of ways.These systems have been extensively studied for topical administration. As a topical vehicle, microemulsions can enhance local or systemic delivery of a drug through a different mechanism [2]. The microemulsion is a good candidate for oral administration of poorly water-soluble drugs due to its ability to enhance drug solubilization. The absorption rate of a drug increases with increasing thermodynamic activity in the vehicle [3].Emulsions play a key role in many of the cosmetics we use today. Much has been written over the years about the formation and stability of these water-dispersed (o/w) or water-dispersed oils Oil systems (without). However, the cosmetic formulator is still trying to understand and create the most cosmetically eloquent and functional products. [11]

Microemulsion:

Microemulsion or Micellar emulsion are dynamic system in which the interface is continuously and spontaneously fluctuating. They are divided into oil in water (O/W), water in oil (W/O) and bi-continuous microemulsion. In W/O



microemulsions, water droplet are dispersed in the continuous oil phase while O/W microemulsion are formed when oil droplet are dispersed in the continuous aqueous phase.

Fig . 1.1 Structure of microemulsion

Nanoemulsion:

Nanoemulsions are very similar to microemulsions, which are dispersions of nanometer-sized particles, but are obtained by mechanical force, unlike micro-emulsions, which form spontaneously. The formulation of nanoemulsions requires the use of two immiscible liquids and an emulsifier. One of the immiscible liquids must be oily and the other must be aqueous in nature, forming the dispersed and aqueous phase.

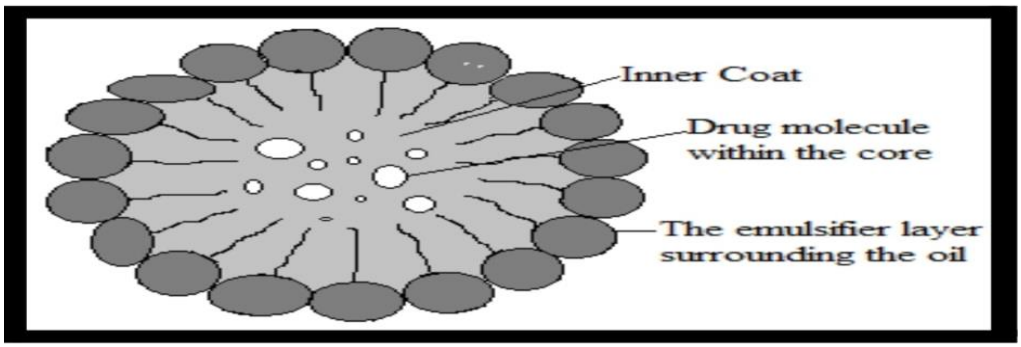


Fig 1.3 : Structure of Nanoemulsion [10]

The high-energy process includes high-pressure homogenization, micro fluidization, and ultrasonic treatment, while the low-energy processes include phase inversion emulsification process and auto-nanoemulsification process [9]

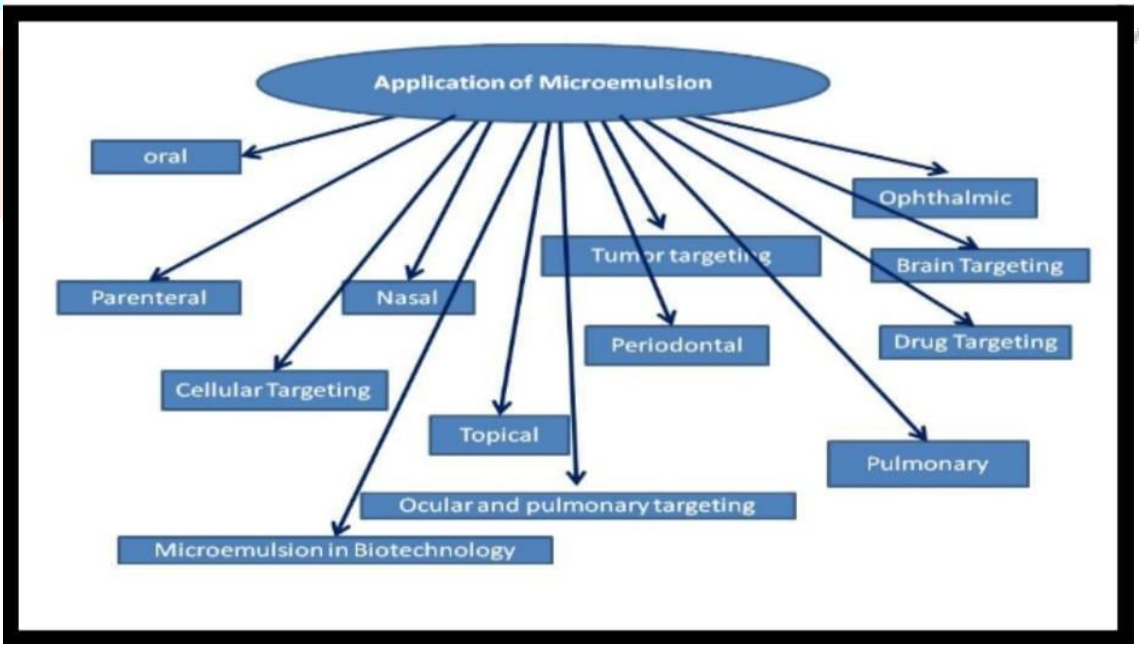


Fig.1.4: Illustration of the application of microemulsion

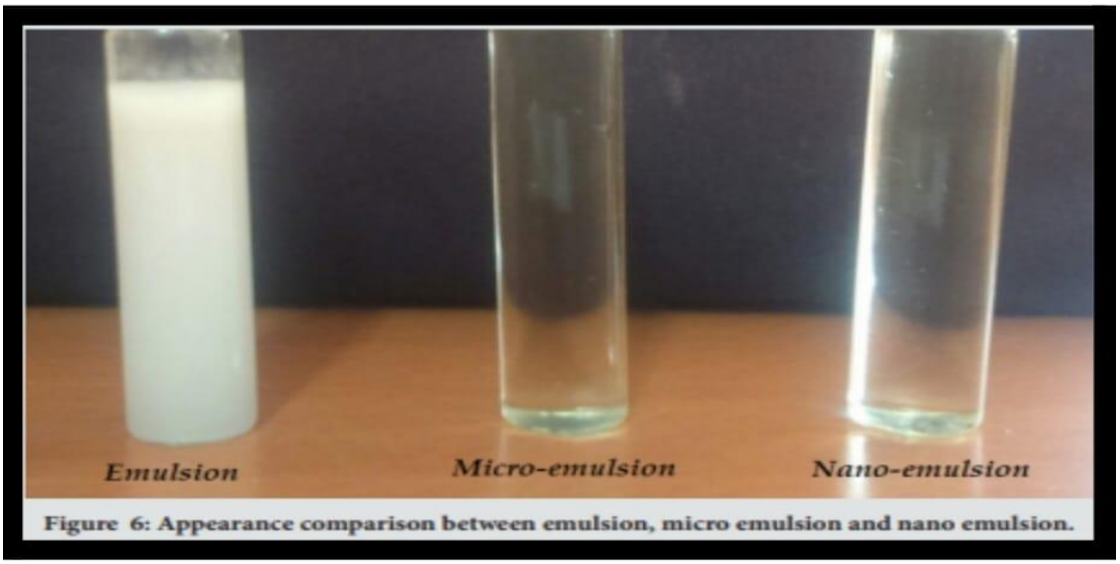


Fig.1.5:Comparison of appearance between emulsion, microemulsion and nanoemulsion.[6]

Types of microemulsion: According to Winsor, there are four types of equilibrium microemulsion phases, these phases are called Winsor phases and are:

A.Winsor I (two-phase system): The upper oil layer is in equilibrium with the lower (o/w) Micro emulsion phase

B.Winsor II (two-phase system): The upper microemulsion (w/o) is in equilibrium with the lower excess water.

C.Winsor III (triphasic system): The middle bicontinuous phase of o/w (called W/O) is in equilibrium with the upper oil phase and the lower water phase.

D.Winsor IV (single phase system): Forms a homogeneous mixture of oil, water and surfactant

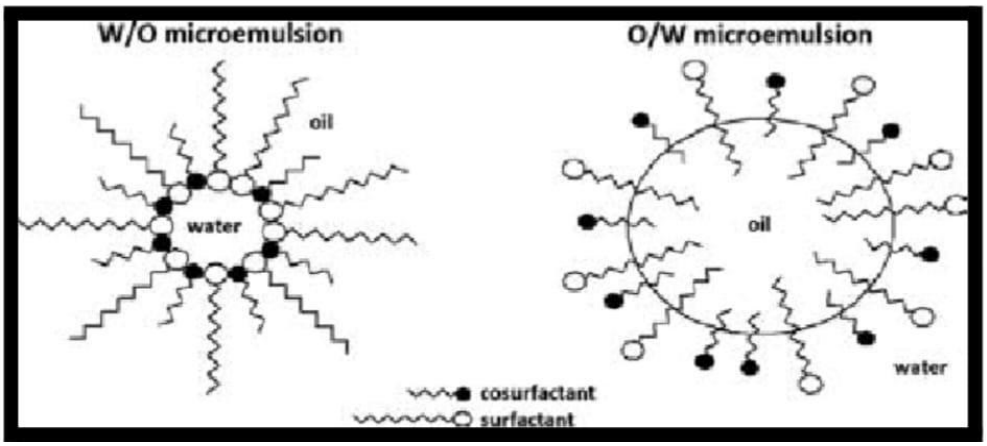


Figure 1.6 O/W and W/O microemulsion structure [7]

COMPOSITION

The main components of the microemulsion system are:

1) Oil phase

2) Surfactant (primary surfactant)

3) Co-surfactant (secondary surfactant)

4) Co-solvent Oil Phase

1. Oil Phase :

The oil phase is the second most important vehicle after water due to its properties to solubilize lipophilic drug molecules and enhance absorption through the lipid layer present in the body.

Example

- Saturated fatty acids: lauric, myristic and capric acids.
- Unsaturated fatty acids: oleic, linoleic and linolenic acids.
- Fatty acid esters: ethyl or methyl esters of lauric, myristic and oleic acids.

2. Surfactants:

During preparation of the microemulsion, the surfactant must be able to reduce the interfacial tension as close to zero as possible to facilitate the dispersion of all components. These surfactants can be:

- Nonionic
- Anionic
- Cationic
- Zwitterionic Example
- Polyoxyl 35 castor oil (Cremophor EL)
- Polyoxyl 40 hydrogenated castor oil (Cremophor RHCo surfactants)

3.Co-surfactants:

It was investigated that high concentrations of single-chain surfactants are required to lower the o/w interfacial tension to a level which allows spontaneous formation of a microemulsion.

Example

- Short chain alcohols such as ethanol to butanol

• Short chain glycols such as propylene glycol

4. Co-Solvents:

Co-solvents are organic solvents such as ethanol, propylene glycol (PG) and polyethylene glycol (PEG) that help dissolve relatively high concentrations.

Table 1.1: Commonly used components of Microemulsion [6]

components	Example
Oils	Saturated fatty acid-lauric acid, myristic acid, capric acid linoleic acid, linolenic acid Fatty acid ester-ethyl or methyl esters of lauric, myristic and oleic acid. Example: (GlycerylMono-anddicaprate isopropylmyristate, sunflower oil, soyabean oil.
Surfactants	Polyoxyethylene/Polysorbate/Tween 20,40,60,80,; Sorbitan Monolaurate (Span), Soybean lecithin, egg lecithin, lyso lecithin, Sodium dodecyl sulphate (SDS), Sodium bis (2–ethylhexyl) sulphosuccinate (Aerosol OT), Dioctyl sodium sulphosuccinate.
Co-surfactants	Ethanol, propanol, Isopropanol, butanol, pentanol, hexanol, sorbitol, n–pentanoic acid, n–hexanoic acid, 2-aminopentane, 1,2-butanediol, Propylene glycol. Cremophor RH40 (polyoxyl 40 hydrogenated castrol oil), Plurololeique (polyglyceryl–6–dioleate).

Types Of Method of preparation of microemulsion:

1.High energy emulsification method:

Ultra sonication and high pressure homogenization.

2. Low energy emulsification:

Phase inversion temperature method, solvent displacement method and phase inversion composition method.

3. High-Pressure Homogenization:

Specially designed high- pressure homogenization instrument is used to produce nano sized particles. At very high pressure (500 to 5000 psi), oil phase and water phase are allowed to force through small inlet orifice.34 Hence extremely small size particles are created due to strong turbulence and hydraulic shear. But this method requires high temperature and energy. Pressure, homogenization cycles are directly responsible for particle size.35 Higher the pressure and higher the homogenization cycles, smallest is particle size. This method is easy to scale up.

4. Microfluidization:

In this method also specially designed device called as microemulsion.

Fluidizer is used to create high-pressure (500 to 20000psi). Initially prepare coarse emulsion of by mixing oil and water phase. This device consists of interaction chamber of small micro channels through which coarse emulsion is forced to an impingement area to form nano size fine particles followed by filteration to obtain uniform particles.

5. Ultrasonication:

This method is based on principle that when coarse emulsion is in ultrasonic field and external pressure is increased, cavitations threshold also increases to limit where fine nano size particles are formed.

6. Phase inversion method:

This method uses principle of phase inversion temperature which is the temperature at which phase transition occurs. Low temperature favours O/W emulsions and high temperature favours W/O emulsion. Rapid cooling and heating cycles produces fine particles. Non-ionic surfactant like polyoxyethylene becomes lipophilic at high temperature and hydrophilic at low temperature due to dehydration of the polymer chain.

7. Spontaneous Emulsification:

This method is simple and uses volatile organic solvent composition of oil, water, lipophilic and hydrophilic surfactant. This composition is allowed to mix homogenously by magnetic stirring. Then evaporate the water-miscible solvent under vaccum to obtain nanoemulsion.

8. Solvent Evaporation Technique:

In this technique, initially mix drug with organic solvent using suitable surfactant and prepare O/W emulsion by mixing continuous phase. Then evaporate organic solvent under vacuum or heating or at atmospheric conditions to obtain microspheres loaded with drug followed by centrifugation or filtration.

9. Hydrogel Method:

This method shares similarity with solvent evaporation method. High shear forces are used to form nano-emulsion of drug- solvent which is miscible with the drug anti-solvent [3]

Advantages of Microemulsion:

1. Microemulsions are easily prepared and require no energy contribution during preparation this is due to better thermodynamic stability.
2. Microemulsions have low viscosity compared to primary and multiple emulsions.
3.The formation of micro-emulsion is reversible. They may become unstable at low or high temperature but when the temperature returns to the stability range, the micro-emulsion refo-rms.

4. The use of micro-emulsion as delivery systems can improve the efficacy of a drug, allowing the total dose to be reduced and thus minimizing side effects.

5. Microemulsion easy to prepare and require no significant energy Contribution during preparation this is due to better thermodynamic stability.

6. The dispersed phase, lipophilic or hydrophilic (O/W, or W/O micro-emulsions) can act as a potential reserves wire of lipophilic or hydrophilic drugs, respectively.

Disadvantages of Microemulsion:

1.Microemulsions are thermodynamically stable system and allow emulsification of the system.

2. Require large amount of Surfactants for stabilizing droplets.

3. Micro-emulsion stability is influenced by environmental parameters such as temperature and pH.

4. Require large amount of S/Cs for stabilizing droplets.

5. The surfactant should be nontoxic for use in pharmaceutical applications.

6. Having limited solubilizing capacity for high melting substances.

Theories of microemulsion formation:

There are some theories of micro emulsion formation such as

1. Interfacial or mixed film theories.
2. Solubilisation theories.
3. Thermodynamic treatments.

   The free energy of micro emulsion formation can be considered to depend on the extent to which surfactant lowers the surface tension of the oil–water interface and the change in entropy of the system such that

$$\Delta Gf = \gamma \Delta A - \Delta Ts$$

: Where ΔG is the free energy of formation, γ is the surface tension of the oil–water interface, DA is the change in interfacial area on microemulsification [13]

Different Delivery Routes for Microemulsion and Recent Development:

(A)Oral Administration:

Micro emulsion formulations offer several advantages over the traditional oral formulation for oral administration, including increased absorption, improved clinical efficacy and reduced drug toxicity. The principle of this type of delivery was developed from a self-emulsifying drug delivery system "SEDDS", SEDDS is a mixture of oil and a surfactant containing drug that spontaneously forms a micro emulsion of oil in water in aqueous media with gentle agitation. The absorption of SEDDS is affected by several factors, including the presence of bile salts. The amount of bile salts present is incorporated into the surfactant layers of the emulsion droplets and ultimately leads to malabsorption of the drug.

(B)Delivery through the skin:

This is the oldest route of administration for which the micro emulsion technique was used. When administered transdermally, the goal of the dosage form is to maximize flux through the skin into the systemic circulation. Successful transdermal administration of ketoprofen, apomorphine, estradiol and lidocaine using microemulsions has been reported. Human skin irritation studies were performed with a lecithin microemulsion gel and with lecithin liposomes. Dermal drug delivery may have advantages over other methods for several reasons, one of which is that it avoids first-pass hepatic drug metabolism and associated toxic effects. The other advantage is the direct delivery of the drug to the affected organ. Traditionally, vaccines have been administered by needle injection. Topical immunization through intact skin with protein- or DNA-based vaccines has recently attracted much attention.

(C)Ocular Delivery:

The ocular route has been considered as one of the promising routes for using the microemulsion technique. The transparency of microemulsion formulations makes them more suitable for ocular applications. Despite their low bioavailability, eye drops are the most common form of administration via the eye. Reported a new microemulsion vehicle for topical ocular delivery of dexamethasone. Because of their unique properties and numerous advantages, microemulsions are promising systems for the topical delivery of ophthalmic drugs. ME can increase the water solubility of the drug and improve the absorption of the drug in the eye. The microemulsion system showed acceptable physicochemical behavior and good stability for 3 months.

(D)Intravaginal Administration:

Gel micro emulsions have been used as vaginal spermicides and intravaginal drug delivery vehicles. Novel gel microemulsions (GM) have been described as non-toxic, dual-purpose intravaginal spermicides that can be used as delivery vehicles for lipophilic drug substances that target sexually transmitted pathogens. D'Cruz etal.These GMs, which comprise an oil-in-water microemulsion and polymeric hydrogels, were designed to solubilize lipophilic antiviral/antimicrobial agents and demonstrated rapid spermicidal activity in human sperm.

(E) Parenteral Administration:

The parenteral administration (particularly via the intravenous route) of drugs with limited solubility is one of the major problems in the industry due to the extremely small amount of drug actually delivered to the target site. Microemulsion formulations have distinct advantages over macro emulsion systems when administered parenterally; because fine-particle microemulsions are excreted more slowly than coarse-particle emulsions and therefore have a longer residence time in the body. Both O/W and W/O microemulsions can be used for parenteral administration. Pharmaceutical peptide and protein drugs are very potent and specific in their physiological functions and difficult to administer orally. Due to their low bioavailability, most protein drugs are only available as parenteral formulations.

(F) Periodontal Delivery:

Due to low viscosity systems, the microemulsion can be easily injected with a syringe, and after injection, transitions to the crystalline phase, then undergoes a thickening transition, thus effectively localizing in a given area within the periodontal pocket. The systems have developed an ethyl laurate-based microemulsion system with Tween 80 as a surfactant, propylene glycol, and ethanol as cosolvents for the intranasal administration of diazepam. Diazepam, a practically water-insoluble drug, showed a high solubility of 41 mg/ml in a microemulsion consisting of 15% ethyl laurate, 15% H2O and 70% (w/w) surfactant/cosurfactant (Tween 80:propylene glycol: ethanol in a weight ratio of 1 :1:1). Nasal absorption of diazepam from this microemulsion was found to be fairly rapid. Microemulsion in aerosol form Peptides and proteins can be dissolved in the aqueous phase of these aerosolizable microemulsions to facilitate delivery to the lungsH) Oral Administration: The buccal route can be used for drug delivery to have both a local and systemic effect a promising avenue for drugs that undergo rapid biotransformation. Aguirre

et al. reported that mometasone furoate microemulsion is effective in the treatment of erosive ulcerative oral lichen planus (OPL)[8].

Different tests of microemulsion:

1. Mean Droplet Size Determination:

The mean droplet size distribution and polydispersion index (PDI) of azelaic acid-loaded formulations were measured using a Malvern Zetasizer 3000HSA equipped with laser diffraction (Malvern Panalytical, Malvern, UK). Three milliliters of test samples were loaded into a cuvette and placed in the dispersion chamber. The light scattering intensity of the helium-neon laser was set at an angle of 90° and a wavelength of 633 nm. LVDV-II, Brookfield Ametek, USA).

2. Determination of viscosity:

The analyzed samples were placed on the conical plate and heated to 37◦C for three minutes with a thermostatic pump. Readings were recorded 30 s after the reading reached 20 rpm. In Vitro Skin Permeation Study All experiments in this study were approved .The committee confirmed that all experiments followed the guidelines of the Data Lines and Laboratory Maintenance Guide. For the in vitro skin permeation experiment, the modified transdermal Franz diffusion cell was used to determine the permeability of formulations loaded with azelaic acid. The recipient cell contained 20 ml of phosphate buffer pH 7.4 with 30% ethanol. The effective diffusion area of the cell was 3.46 cm2 and the drug solution also contained30% ethanol. One ml of the test sample was placed in the donor cell, which was then sealed with parafilm. At predetermined intervals. All experiments were repeated in triplicate. The mobile phase consisted of a solution of phosphoric acid, pH 3.0, and acetonitrile eluted at a flow rate of 0.08 ml/min through a stationary phase. The precision of the coefficient of variation and the precision of the relative error were less than 3.67% and 4.22 %. Pharmacodynamic Evaluation Twenty-four Balb/c mice were randomized into four groups for a single dose of test formulations (Formulation blank, Formulation containing 5% drug, Commercial product, and untreated). Skin Irritation Determination Skin irritation caused by the tested formulations was evaluated by histological microscopy. Tissue samples were fixed, rinsed with running distilled water, dehydrated using with a graded series of ethanol solution. The tissue samples were cut into sections of 20 µm, rehydrated, and stained

with and eosin for histological evaluation. Stability of Azelaic Acid-Loaded Formulation Determination to quickly evaluate the stability of the M3 microemulsion, thermodynamic stability tests including centrifugation and freeze-thaw cycle methods were performed. Briefly, the selected drug-loaded formulation was centrifuged at 3,500 rpm for 30 min and three cycles conducted between freeze temperature (−21 ◦C) and room temperature 25 ◦C with storage at each temperature for no less than 24 h. The phase separation, transparency, and precipitation of drug from formulations were investigated.

3. Physicohemical Characterization :

The composition, droplet size and PDI are shown in Table 1. The PDI values of all formulations were less than 0.3, indicating that the mixtures achieved homogenization. Increasing the ethanol concentration increased the size of the surfactant) were submicron. The phenomenon can be attributed to the higher viscosity of PG, which increases the viscosity of the microemulsion system . In vitro permeation study The in vitro permeation time profiles of the azelaic acid-loaded formulations and the control group, drug solution with 30% ethanol, through rat skin are shown in For the control group, the lag time (first time the drug is detected) was about 8 hours and the accumulated amount after 24 hours Transport through the skin of the rat. By using microemulsions as the vehicle, the residence time was reduced to 2~6 h and the accumulated amounts of azelaic acid increased significantly. The results were consistent with previous reports indicating that microemulsions can improve the permeability of compounds.

4. Pharmacodynamic evaluation:

In this study, cutaneous polymorph nuclear leukocyte inflammation induced by croton oil was used to evaluate the efficacy of the experimental formulations and the Ear swelling data were taken as an index of inflammation. As shown in inflammation was evident after croton oil treatment. Without treatment, the swelling subsided over time but was still there after 24 hours. The application of white M3 did not improve the inflammatory state compared to the control group. The micro emulsion's nanocarrier could improve the permeability of the drug through the skin.

5. Skin irritation :

On-significant edema and erythema were found in the blank microemulsion of the skin sections treated with the M3 formulation compared to distilled water. Treated group of Observations indicated that the designed microemulsion formulation appeared to be a safe vehicle for topical application of azelaic acid.

Eg: Stability of the Azelaic Acid-Loaded Formulations:

Formulations did not change in terms of phase separation and transparency, showing that the microemulsion loaded with azelaic acid possessed thermodynamic stability furthermore, no drug precipitation was observed. After 30 days storage at 25◦C, the azelaic acid content was 96.3 ± 4.16% and the droplet size and viscosity of the formulation did not change significantly, indicating that the tested azelaic acid-loaded formulations were considered stable.

New Development:

Environmentally sensitive drug delivery systems are an exciting development, and phase changes that occur after delivery, triggered by changes in temperature, pH, or ionic strength, can be particularly useful. An example of such behavior involves the phase transformation of an inverse micellar lecithin solution in IPM to a lamellar liquid crystal. In this case, the transition was triggered by contact of the reverse micellar solution with a biological aqueous phase, resulting in the controlled release of the anti-inflammatory fenoprofen. Similar behavior was recently observed with the use of thermosetting micro emulsions as delivery systems for periodontal anesthesia.In this case, a liquid block copolymer micro emulsion containing lidocaine and prilocaine was developed to form a gel after in vivo administration into the periodontal pocket [12].

Conclusion:

Microemulsions are exceptionally stable systems that the cosmetic formulator should take into account. In general, they are more difficult to formulate compared to regular emulsions due to the specificity of the formulation and in many cases the order of mixing. An approach to support the development of such systems in an orderly and rapid timeframe is outlined.

This is one of the recent advances in the microemulsion delivery system. Structured self-assembling liquids are considered to be efficient micro reactors for organic and enzymatic reactions.

This document covers most applications related to heterogeneous catalysts made from microemulsions Method. These catalytic materials have been used in a variety of applications such as research in this area is increasing and advances are expected to result from fruitful collaborations with scientists in the fields of physical chemistry, materials science, colloid chemistry, and catalysis.Catalyst preparation is challenging, catalysts prepared from microemulsions show very interesting properties in certain laboratory-scale reactions.

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