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A REVIEW ON MICROEMULSION BASED GEL: AN INNOVATIVE APPROACH FOR TOPICAL DELIVERY OF HYDROPHOBIC DRUG

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ABSTRACT

In current scenario, an augmentation in topical formulations by virtue that it can be prepared by altering physicochemical properties as well as furnishing more desirable localized action. It is imperious to adhere patient to topical formulations in dealing with chronic skin diseases like Skin infections, Eczema and psoriasis. One of the modernistic technology in Novel Drug Delivery System used topically is Microemulsion based Gel carry virtue of bi-fold control release i.e. microemulsion as well as gel. For hydrophobic drugs, Microemulsion based gel has been emanated as a felicitous topical drug delivery system and demonstrated as fortune for dermal care and cosmetology. When microemulsion is included in gel, its stability is also raised. Microemulsions have been confirmed for increment in cutaneous absorption of both lipophilic and hydrophilic API's when correlated to conventional vehicles. This versatile, thermodynamically stable, colloidal dispersion of water and oil is stabilized by surfactant and co-surfactant. It is prepared by different polymers, emulsifier and owing to the gelling capacity of these compounds give improvement to stable emulsions as surface and interfacial tension is reduced while at that moment increment in the viscosity of the aqueous phase. For dermatological treatment, microemulsion based gel has certain beneficial properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water soluble, longer shelf life, bio-friendly, transparent & pleasing appearance. In present review, we discussed certain advantages of microemulsion based gel in pharmaceuticals, along with its preparation and characterization.

KEYWORDS: Microemulsion, Gel, Topical delivery, hydrophobic drug.

INTRODUCTION

In last few decades, the treatment of several diseases has been accomplished by administering drug to human body via various routes, namely, oral, sublingual, rectal, parental etc. The topical drug delivery system is generally used in where other systems of drug administration fail or it is mainly used in local skin infection like fungal infection, acne, psoriasis. Topical drug delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorder. In these modern days, pharmaceutical research work is focused to fulfil the therapeutic needs of patients. Most of active pharmaceutical ingredients developed are hydrophobic in nature, so to develop new drug delivery system microemulsion has good impact on effective delivery of hydrophobic drugs.[1]

Human skin is a uniquely engineered organ that permits terrestrial life by regulating heat and water loss from the body whilst preventing the ingress of noxious chemicals or microorganisms. Many widely used topical agents like ointments, creams and lotions have numerous disadvantages. They are usually very sticky causing uneasiness to the patient when applied. Moreover, they also have less spreading coefficient and need to apply with rubbing. They also exhibit the problem of stability, due to all these factors, within the major group of semisolid preparations; the use of transparent gels has increased both in cosmetics and in pharmaceutical preparations.[2]

Topical gels are transparent or translucent semisolid formulations containing a high ratio of solvent/gelling agent. Gels are defined as semi-rigid system in which the movement of the dispersing medium is restricted by interlacing three-dimensional networks of particles or solvated macromolecules of the dispersed phase. They are non-invasive and have patient compliance, less greasy, easily removed from the skin, cost effective, reduction of doses as compare to oral dosage forms, localized effect with minimum side effects, improving drug bioavailability, reducing dose frequency and stabilizing drug delivery profiles.[3,4]

In spite of many advantages of gels, a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation microemulsion based approach is being used, so that even a hydrophobic therapeutic moiety can enjoy the unique properties of gels. First, oil-in water microemulsion is prepared, which is then gelled by mixing with a gelling agent.

Emulsified gel is stable one and superior vehicle for hydrophobic or poorly water soluble drugs. In short microemulsion based gels are the combination of microemulsion and gel.[5]

❖ **Advantages of Topical Drug Delivery Systems**[6]

- ✓ Avoidance of the first pass metabolism.
- ✓ Convenient and easy to apply.
- ✓ Avoidance of risks and inconveniences of the intravenous therapy and of diverse conditions of absorption like pH changes, presence of enzymes, gastric emptying time.
- ✓ Easily terminate the medications, when needed.
- ✓ Deliver drug more selectively to a specific site.
- ✓ Avoidance of the gastrointestinal incompatibility.
- ✓ Providing utilization of drugs with short biological half-life, narrow therapeutic window.
- ✓ Improved patient compliance.
- ✓ Provide suitability for self-medication.
- ✓ Achievement of effectiveness with lower total daily dose of drug by continuous drug input.
- ✓ Avoids fluctuation in drug levels, inter- and intra-patient variations.
- ✓ A quite large area of application in comparison with buccal or nasal cavity.
- ✓ Ability to deliver drugs more selectively to a specific site.

❖ **Disadvantages of Topical Drug Delivery System**[5]

- ✓ Skin irritation of contact dermatitis may occur due to the drug and excipients.
- ✓ Possibility of allergenic reactions.
- ✓ Enzyme in epidermis may denature the drug.

ANATOMY AND PHYSIOLOGY OF THE SKIN[7, 8, 9]

Skin is one of the most readily accessible organs on human body for topical administration and is the main route of topical drug delivery system. The total area of skin is about 20 square feet. The skin protects us from microbes and the elements help to regulate body temperature and permit the sensations of touch, heat and cold. The pH of the skin varies from 4 to 5.6. Sweat and fatty acid secreted from sebum influence the pH of the skin surface. The skin is composed of three layers:

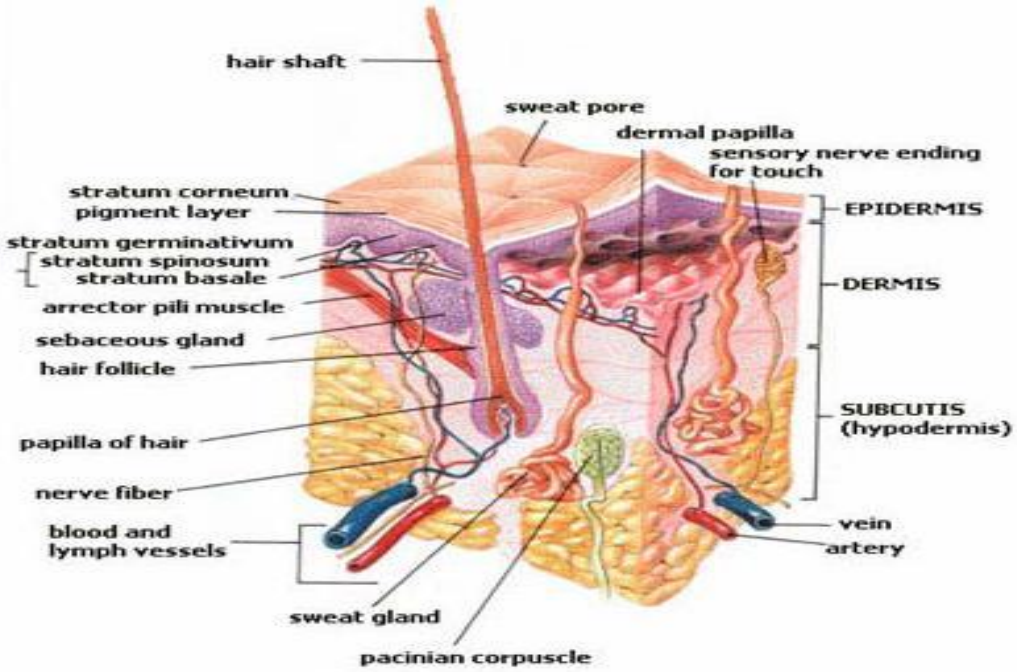

Figure 1: Skin structure.[9]

1. The epidermis

- ✓ Outer layer of the skin
- ✓ Composed of stratified squamous epithelial cells
- ✓ Approximately 50-100µm thick
- ✓ 90% water content
- ✓ No capillary and no blood vessel

Layers of epidermis are

- Stratum corneum (horny layer)
- Stratum germinativum (growing layer)
- Malpighion layer (pigment layer)
- Stratum spinosum (prickly cell layer)
- Stratum lucidum
- Stratum granulosum (granular layer)

2. The dermis

- ✓ Just beneath the epidermis
- ✓ Composed of network of collagen & elastic fibers embedded in a mucopolysaccharide matrix, which contain blood vessel lymphatic & nerve endings
- ✓ Approximately 2000-3000µm thick

3. The subcutaneous fat tissues

- ✓ Sheet of fat containing areolar tissue, known as superficial fascia
- ✓ Attaching the dermis to underlying structure
- ✓ Composed of loose textured, white, fibrous connective tissue containing blood and lymph vessels, secretary pores of the sweat gland and cutaneous nerves.

Mechanism of Drug Absorption[10]

Permeation of a drug involves the following steps

1. Sorption of a penetrate molecule on surface layer of stratum corneum.
2. Diffusion through it and viable epidermis and finally reach to dermis.
3. The molecule is taken up into the microcirculation for systemic distribution.

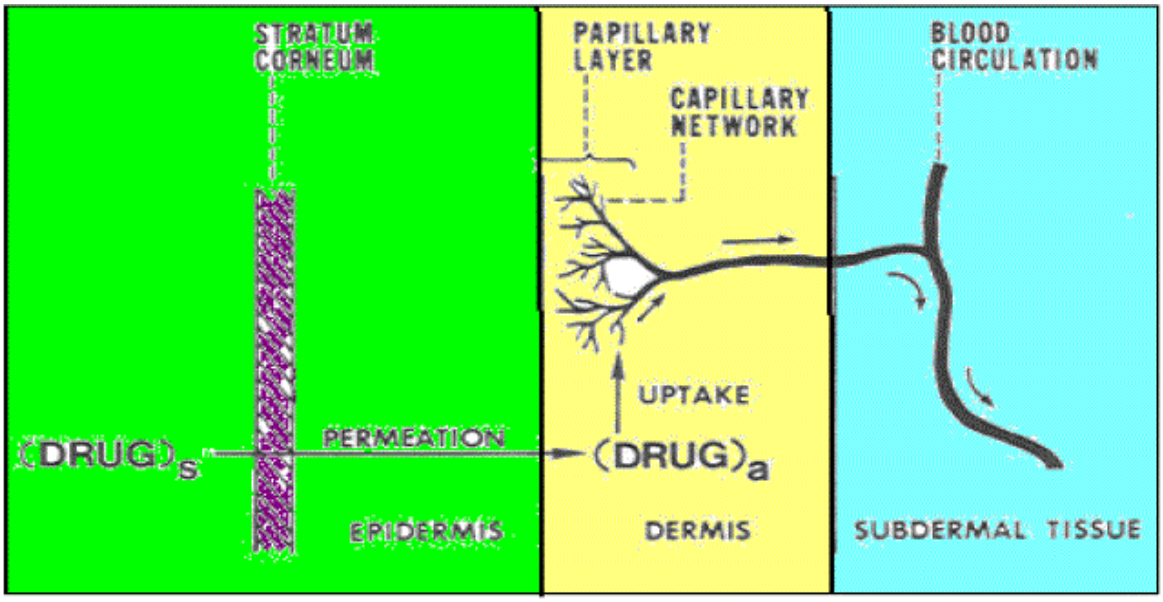

Figure 2: A multilayer skin model showing sequence of skin permeation of drug.[10]

- **Permeation pathways**[10]

A molecule may use two diffusional routes to penetrate normal intact skin.

1. Appendageal route: Appendageal route comprises transport via sweat glands and hair follicles with their associated sebaceous glands.

2. Epidermal route: For drugs, which mainly cross-intact horney layer, two potential micro routes of entry exists, the transcellular and intercellular pathways.

i. Trans-cellular: Passage of drugs across the epithelial cells.

ii. Intercellular: Transport of drugs through junction between the epithelial cells.

- **Factors Affecting Topical Absorption of Drug**[11]

➢ **Physiological Factors**

✓ Skin thickness
✓ Lipid content
✓ Density of hair follicles
✓ Density of sweat glands
✓ Skin pH
✓ Blood flow
✓ Hydration of skin
✓ Inflammation of skin

➢ **Physiochemical Factors**

✓ Partition coefficient
✓ Molecular weight (<400 daltons)
✓ Degree of ionization (only unionized drugs gets absorbed well)
✓ Effect of vehicles

INTRODUCTION OF MICROEMULSION BASED GEL

- The term "microemulsion" refers to a thermodynamically stable, isotropic clear dispersion of two immiscible liquids, such as oil and water, which is stabilized by an interfacial film of surfactant molecules.[12]

The microemulsion concept was introduced in early 1940s by Hoar and Schulman who generated a clear single-phase solution by titrating a milky emulsion with hexanol. They prepared the first microemulsion by dispersing oil in an aqueous surfactants solution and adding an alcohol as a co-surfactant, leading to transparent stable formulation.[13]

When micro-emulsion and gel are mixed together to form single dosage forms, the obtained formulations is named as microemulsion based gel, also called as microemulsion based gel, having the dual benefits as well as micro-emulsion.[12, 13]

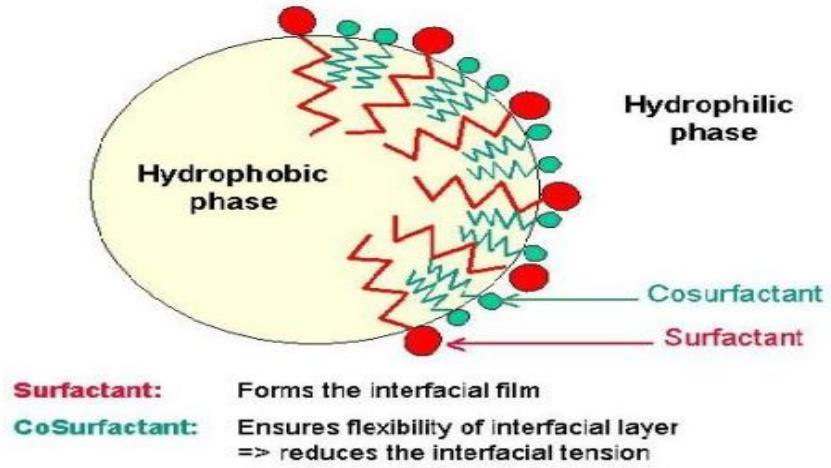

Figure 3: Microemulsion Structure.[14]

- **Components of Microemulsion based Gel[12,13,15,16]**

1. Oil phase: The selection of oil is based on the nature of the drug as well as the route of administration. The screened oil should have solubilization potential for the drug. The oil influences the curvature and has the capability to swell the tail group of surfactant. Saturated and unsaturated fatty acids have penetration enhancing activity of their own. Amongst unsaturated fatty acids, oleic acid is an effective skin penetration enhancer.

Recent trend is towards use of semi-synthetic oils that are more stable than their natural counterparts. Poorly aqueous soluble drugs need to have solubility in dispersed oil phase to form efficient o/w microemulsion system. Even with increase in oil content in o/w microemulsion leads to increase in droplet size.

2. Aqueous phase: The aqueous phase may contain hydrophilic active ingredients and preservatives. Water is most commonly used as an aqueous phase.

3. Surfactants: The primary use of surfactant is to lower the interfacial tension to a very small value which will facilitates dispersion process during the preparation of the microemulsion and provide a flexible film that can readily deform around the droplets and be of the appropriate lipophilic character to provide the correct curvature at the interfacial region. Surfactants used to stabilize microemulsion system may be.

I. Non-ionic, II. Zwitterionic, III. Cationic, or IV. Anionic

In the formation of microemulsion the surfactant may be ionic or non-ionic, which determines the stabilizing interactions of the hydrophilic end of the surfactant with the

aqueous phase. Thus, while a non-ionic surfactant is stabilized by dipole and hydrogen bond interactions with the hydration layer of water on its hydrophilic surface, an ionic surfactant is additionally stabilized by the electrical double layer. Thus, the effect of salt concentration on the stability of an emulsion or a microemulsion is more profound in the case of ionic surfactant than non-ionic surfactants. However, for pharmaceutical applications, ionic surfactants are not preferred due to toxicological concerns. Non-ionic surfactants are generally considered to be acceptable for pharmaceutical preparation.

It is generally accepted that low HLB (3-6) surfactants are favoured for the formulation of w/o microemulsion, whereas surfactants with high HLB (8-18) are preferred for the formation of o/w microemulsion. Surfactants having HLB greater than 20 often require the presence of cosurfactants to reduce their effective HLB to a value within the range required for microemulsion formation.

4. Co-surfactants: It has been found that single-chain surfactants alone are unable to reduce the o/w interfacial tension sufficiently to enable a microemulsion to form. The presence of co-surfactants allows the interfacial film sufficient flexibility to take up different curvatures required to form microemulsion over a wide range of composition. If a single surfactant film is desired, the lipophilic chains of the surfactant should be sufficiently short or contain fluidizing groups (e.g. unsaturated bonds). Short to medium chain length alcohols (C3-C8) are commonly added as co-surfactants which further reduce the interfacial tension and increase the fluidity of the interface. Typical co-surfactants are short chain alcohols (ethanol to butanol), glycols such as propylene glycol, medium chain alcohols, amines or acids.

The role of a co-surfactant is as following

1. Increase the fluidity of the interface.
2. Destroy liquid crystalline or gel structure which would prevent the formation of microemulsion.
3. Adjust HLB value and spontaneous curvature of the interface by changing surfactant partitioning characteristic.

Table 1: Components of Microemulsion Based Gel.

Oil	Surfactant	Co-surfactant	Gelling Agent
Ethyl oleate Mineral oil IPM Decanol Oleic acid Vegetable oils (coconut oil,sunflower oil,soyabean oil,olive oil)	Polysorbate (Tween 80 and Tween 20) Lauromacrogol 300, Lecithins Decylpolyglucoside (Labrafil M 1944 LS), Polyglyceryl-6-dioleate(PlurolOleique, Dioctyl sodium)	Sorbitanmonooleate, Sorbitanmonostearate, Propylene glycol, Propylene glycol monocaprylate (Capryol 90), 2-(2-ethoxyethoxy) ethanol(Transcutol P)	Carbopol 934 Carbopol 940 HPMC K100 M HPMC K15 M Sodium CMC

- **Method of preparation of microemulsion**

A. Phase Titration Method (Spontaneous emulsification method)[13]

Microemulsions are prepared by the spontaneous emulsification method (phase titration method) and can be depicted with the help of phase diagrams. Construction of phase diagram is a useful approach to study the complex series of interactions that can occur when different components are mixed. The understanding of their phase equilibrium and demarcation of the phase boundaries are essential aspects of the study. As quaternary phase diagram (four component system) is time-consuming and difficult to interpret, pseudo ternary phase diagram is often constructed to find the different zones including microemulsion zone, in which each corner of the diagram represents 100% of the particular component (Figure 5). The region can be separated into w/o or o/w microemulsion by simply considering the composition that is whether it is oil rich or water rich. Observations should be made carefully so that the metastable systems are not included.

Construction of Pseudoternary phase diagram[17]

Pseudoternary phase diagrams are constructed to obtain the concentration range of oil, surfactant, co-surfactant, and water for microemulsion to enhance its permeability through the skin. It provides information on the boundaries of the different phases as a function of composition variables and temperatures, and, more important structural organization can also be inferred. One approach to characterizing these multicomponent systems is by means of pseudo ternary diagrams that combine more than one component in the vertices of the ternary diagram. Surfactant and co-surfactant get preferentially adsorbed at the interface, reducing the interfacial energy as well as providing a mechanical barrier to coalescence. Therefore, the

selection of oil and surfactant and the mixing ratio of oil to surfactant/ co-surfactant play an important role in the formation of microemulsions.

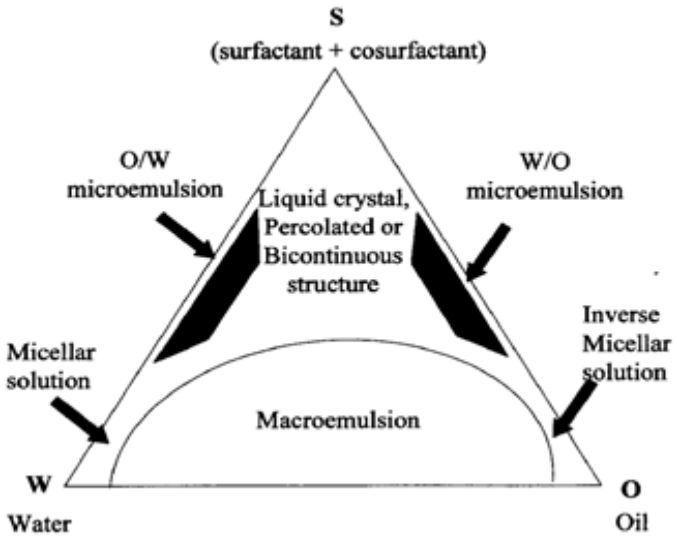

Figure 4: Pseudoternary phase diagram.

B. Phase Inversion Method[14]

Phase inversion of microemulsion happens upon addition of excess of dispersed phase. Phase inversion leads to radical physical changes as change in particle size that alters drug release. During cooling, this system crosses the point of zero spontaneous curvature and minimal surface tension, prompting the formation of finely dispersed oil droplets. Microemulsions can be prepared by controlled addition of lower alkanols (butanol, pentanol and hexanol) to milky emulsions to produce transparent solutions comprising dispersions of either o/w or w/o or colloidal dispersions. The lower alkanols are called co-surfactants. They lower the interfacial tension between oil and water sufficiently low for almost spontaneous formation.

- **Advantages of Microemulsion based Gel**[18, 19]

✓ **Incorporation of hydrophobic drugs:** Most of the hydrophobic drugs cannot be incorporated directly into gel base because solubility act as a barrier and problem occurs during the release of the drug, mainly class IV drug. Emulgel helps in the incorporation of hydrophobic drugs into the oil phase and then oily globules are dispersed in aqueous phase resulting in o/w emulsion. And this emulsion can be mixed into gel base. This may be proving better stability and release of drug than simply incorporating drugs into gel base. e.g. ketoconazole, fluconazole.

- ✓ **Better loading capacity:** Other novel approaches like niosomes and liposomes are of Nano size and due to vesicular structures may result in leakage and result in lesser entrapment efficiency. But gels due to vast network have comparatively better loading capacity of drug.
- ✓ **Better stability:** Other Transdermal preparations are comparatively less stable than emulgels. Like powders are hygroscopic, creams shows phase inversion or breaking and ointment shows rancidity due to oily base and normal topical emulsion shows creaming effect. Therefore this emulgel does not show any of above problems and gives better stability.
- ✓ **Production feasibility and low preparation cost:** Preparation of emulgel comprises of simpler and short steps which increase the feasibility of the production. There are no specialized instruments needed for the production of emulgels. Moreover, materials used are easily available and cheaper. Hence, decreases the production cost of emulgels.
- ✓ **Controlled release:** Emulgels can be used to prolong the effect of drugs having shorter $t_{1/2}$.

- ❖ **No intensive sonication:** Production of vesicular molecules needs intensive sonication which may result in drug degradation and leakage. But this problem is not seen during the production of emulgels as no sonication is needed.

- ❖ **EVALUATION OF MICROEMULSION[20]**

- **Viscosity:** Brookfield Rotational viscometer is used to measure viscosity.
- **pH:** pH is measured by digital pH meter
- **Drug Content:** API based micro-emulsion is subjected to extract API from microemulsion in appropriate solvent. Suitable dilution is made with solvent and concentration is measured by UV-visible spectroscopic method at its maximum wavelength by keeping solvent as reagent blank.
- **Centrifugation:** This parameter is measured to evaluate physical stability. Microemulsion is centrifuged at ambient temperature and 5000 RPM for 10 min to evaluate the system for creaming or phase separation. System will be observed visually for appearance.
- **Conductivity:** Electric conductivity of micro-emulsion is measured at ambient temperature with digital conductometer.

- **Dilution Test:** If continuous phase is added into microemulsion, it will not be separated into phases. 50–100 times continuous phase dilution of microemulsion will be carried out and visually checked for phase separation and clarity.
- **% Transmittance Measurement:** Micro-emulsion will be diluted to 50–100 times with continuous phase. The %transmittance of formulation is measured using UV-Visible spectrophotometer at a specific wavelength.
- **Zeta potential and Micelle Size analysis:** Micelle size, Size distribution and zeta potential of microemulsion are determined using particle size analyzer.
- **In-vitro-Release Study:** It is carried out using Franz diffusion cell.

❖ **EVALUATION OF MICROEMULSION BASED GEL.**[20]

- **Physical Examinations:** Microemulsion based gel is inspected for their color, homogeneity, consistency, texture, etc.
- **pH:** pH of the 1% aqueous solution of the prepared microemulsion based gels is measured by digital pH meter.
- **Spreadability Measurement:** To determine the Spreadability of microemulsion based gel, 0.5 gm. of microemulsion based gel is placed within a circle of 1 cm diameter pre-marked on a glass plate, over which second plate is placed. A weight of 5 gm is allowed to rest on the upper glass plate for 5 min. The increase in diameter due to microemulsion based gel, the spreading is noted in cm/gm-sec.
- **Syneresis measurement test:** Upon standing; sometimes gel system shrinks a bit and little liquid is pressed out. This phenomenon is known as Syneresis. In this test, microemulsion based gel is put in a cylindrical plastic tube with a perforated bottom which is covered with filter paper (Whatman No. 41). These tubes will then placed in centrifuge tubes and centrifuged for 15 min. The cylindrical plastic tube and liquid which separated from microemulsion based gel is weighed. The percentage of Syneresis is then calculated as.

$$\% \text{ of syneresis} = \frac{\text{weight of liquid seperated from microemulsion based gel}}{\text{total weight of microemulsion based gel before centrifugation}} \times 100$$

- **Rheological study:** Mainly viscosity is determined at 37 ˚C by means of Brookfield Viscometer.
- **Drug content determination:** Drug content in microemulsion based gel is measured by dissolving 1gm of microemulsion based gel insolvent by sonication. Absorbance is measured after suitable dilution at λmax nm using UV spectrophotometer.

- **Tube Test (Extrudability Test):** Force required to measure to extrude material from tube to evaluate microemulsion based gel formulation for extrudability.
- **In-vitro-Release Study:** It is studied using Franz diffusion cell at 37˚C.
- **Drug release kinetics study:** Results of in-vitro release profile obtained for all batches are plotted in models of data treatment as.

• Zero order kinetic model – % CPR Vs time.

• First order kinetic model – log % cumulative drug remaining Vs time.

• Higuchi's model – % cumulative drug released vs. square root of time.

• Korsmeyer/Peppa's model – log % cumulative drug released Vs log time.

• Hixson Crowell model – Cube root of % drug to be remaining Vs Time.

- **Skin Irritation:** It is carried out using Draize-patch test in Rabbit.
- **In-vivo study:** In animal study.

Optimization of Microemulsion based gel.

Accelerated Stability study of optimized microemulsion based gel.

Sample of API loaded microemulsion based gel is sealed in ampoule and then placed in an accelerated stability chamber at40 ˚C ± 5˚C temperature and 70% ±5% RH. Duplicate sample is withdrawn at 1, 2 and 3 months to evaluate their physicochemical parameters. The physical stability is evaluated by visual inspection for physical changes such as phase separation and drug precipitation. Chemical stability is expressed as the content of drug determined by UV visible spectroscopic method at λmax nm.

❖ **Application of Microemulsion Based Gel**[21]

Table 2 - Application of Microemulsion Based Gel.

Category	Active ingredients	Application
Antifungal	Fluconazole, Voriconazole, Miconazole	Reduce fungal infection around the skin
Antiviral	Penciclovir	Treatment of herpes labialis infection
Anti-inflammatory	Ibuprofen Ketoprofen	In initial stage of inflammatory symptoms
Antibiotic	metronidazole	Reduce the bacterial infection and improve healing
Antioxidant	Quercetin	Used in anti-aging and cosmetic products

Marketed product of Emulgel[22, 23]

Table 3: Marketed Formulations.

Product Name	Drug	Manufacturer	Use
Voltarol 1.16% emulgel	Diethaylammonium {-o-[2,6 dichlorophenyl)-amino]-phenyl}-acetate	Novartis	Anti-inflammarory
Diclomax Emulgel	Diclofenac sodium	Torrent pharma	Anti-inflammatory
Miconaz-H-emulgel	Miconazole nitrate, Hydrocortisone	Medical union pharmaceuticals	Topical corticosteroid and antifungal
Avindo gel	Azithromycin	Cosmepharma Laboratories	Antibiotic

CONCLUSION

In the recent years, topical drug delivery system will be used extensively due to better patient compliance. Emulgel is one of the best approaches for the topical drug delivery of hydrophobic drugs and obviously it is a very good technique for drug delivery of combination of both hydrophilic and hydrophobic drugs. Mainly the hydrophobic drug formulation can be developed with microemulsion based gel technique because it contains both oil and aqueous (i.e. gel base) on the other hand hydrogel is not suitable for hydrophobic drugs. Microemulsion based gel have properties of both microemulsion and gels and thus can be used for controlling release rate of drugs with short half-life. Currently, very few marketed microemulsion based gel formulation are available in market however, it offers a vast field for development and research. However, regarding various advantages and future prospective emulgels offer a wide utility in derma care. Due to lack of excessive oily bases and excipients, it shows better drug release and thus could be formulation of choice in various dermatological diseases.

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