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A REVIEW ON: MICROEMULGEL AS A NEW PLATFORM FOR TOPICAL APPLICATION

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ABSTRACT
Topical therapies in cream, ointment, gel and lotion formulation are an important component of dermatological therapeutic armamentarium. They are relatively free of serious side effects. Microemulgel is a mixture of microemulsion and gel, is relatively a new and novel topical drug delivery system which has many advantages and potential uses in dermatology. Microemulgel is one such a unique feature of a topical delivery system for drug make the localized administration and direct acceptability of the drug anywhere in the body through ophthalmic, vaginal, skin and rectal routes. Micro-emulsion based gel is emerging topical delivery systems contain both micro-emulsion as well as gel. Micro-emulsion based gel is either oil in water or water in oil type of micro-emulsion which is gelled by mixing it with suitable gelling agent. Incorporation of micro-emulsion into gel increases its stability and makes it dual control release system. Presence of gel phase makes it a non-greasy, non sticky and smooth appearance which favors superior patient compliance. Despite of gel have a limitation in delivery of hydrophobic drug moiety. This moiety can be overcome by the use of novel drug delivery system i.e. microemulgel. Microemulgel is one of topical drug delivery system that incorporates properties of both gel and micro-emulsion and shows dual release control system. Currently many drugs of antimicrobial, antifungal and non steroidal anti inflammatory class are studied for their topical delivery through microemulgel formulation. Microemulgel prolongs the drug release, increases patient compliance and stability of microemulgel. After the brief study, it can be concluded that the microemulgel appear better and effective drug delivery system as compared to other topical drug delivery system.

KEYWORDS: Microemulgel, Microemulsion, gel and Topical Application.

1. INTRODUCTION[1,2,3,4]
The concept of micro-emulsions was first introduced by Hoar and Schulman during 1940s. It is defined as a system of water, oil and amphiphile which is an optically isotropic and thermodynamically stable liquid micro-dispersion. Micro-emulsion is the vehicle for improving the delivery, efficacy and bioavailability of several drugs. Micro-emulsions are thermodynamically stable transparent, isotropic, low viscosity colloidal dispersions containing oil and water stabilized by an interfacial film consisting of surfactant/co-surfactant. Topical delivery administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Efforts to cure diseases have been leading in the discovery of various drugs, Medicine and delivery systems. Route of administration depends on type and severity of disease. For skin disorders topical route is most preferred. Topical drug delivery system can be defined as direct application of formulation containing medication to the skin to get localized effect of drug.

Topical drug delivery is the potential route to deliver the drug producing low side effect in comparison with any other dosage forms. Drug concentration can be optimized to low concentration due to lack of metabolic elimination of drug before reaching the targeted site. There are many conventional dosage forms for topical applications as ointment, cream, gel, but they shows fluctuation in bioavailability of drugs and are associated with other limitation as gel is limited to deliver the hydrophilic drugs, also ointment are limited for hydrophobic drug, so recently there have been novel approaches in the topical delivery to control the fluctuation of drug and deliver in a controlled manner as per our need and to decrease the limitation associated with conventional preparation also to improve their properties for patient compliance. The new approach in the field of topical drug delivery is introduced to deliver the hydrophilic drug that can enjoy the gelling property and whose rate can be controlled named microemulgel. It is simply where Micro-emulsion of the drug is prepared and that are incorporated in the gel. Microemulgel are transparent and

thermodynamically stable as their droplet size range from 10-100 nm.

While microemulgel, the combined form of micro-emulsion and gel have advantage of both micro-emulsion and gel. Micro-emulgel for dermatological use have several advantages like thixotropic, greaseless, easily spreadable, easily removable, emollient, non staining, long shelf life, bio-friendly, transparent and pleasing appearance.

Anatomy and physiology of skin[4,5,6,10,13]

The skin of average adult body covers surface area approximately 2 m^2 and receive about one third of blood circulating through body. An average human skin surface is mainly contains forty to seventy hair follicles and two to three hundreds of sweat ducts per square meter of skin.

The pH of skin varies from 4 to 5.6. Sweat and fatty acid secreted from sebum influence the pH of skin. The skin consists of four distinct layers of tissues, namely, nonviable epidermis, viable epidermis, viable dermis and subcutaneous connective tissues (Figure 1).

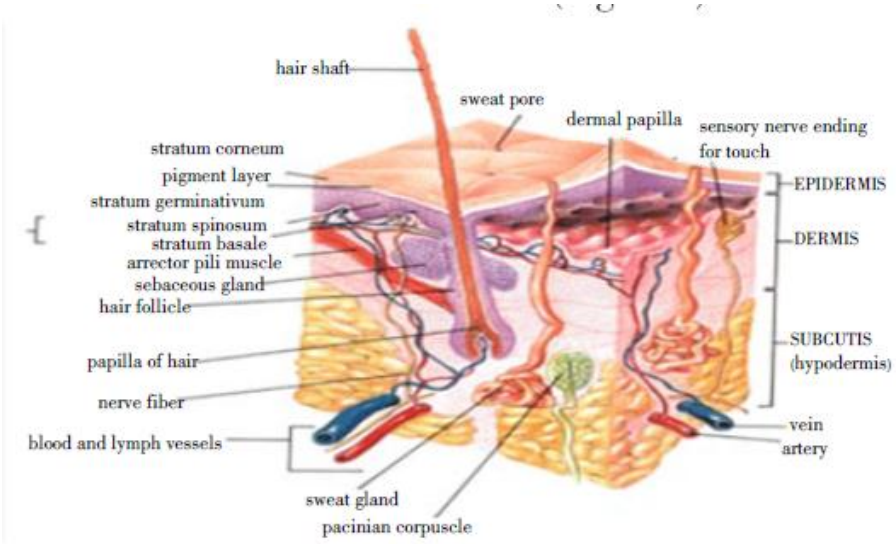


Figure 1: Anatomy of skin.

The skin can be considered to have four distinct layers of tissue as follow.

1. Non-viable epidermis
2. Viable epidermis
3. Viable dermis
4. Subcutaneous connective tissue

1) Epidermis

The outside layer of the skin is known as "Epidermis", which is approximately 150 µm thick The epidermis (outer layer) contains no blood vessels and is divided into five layers. Cells move from the base of the epidermis up to the surface, changing shape and structure as they go. Glucose is the source of energy for lower portions of epidermis and lactic acid, produce at the end of metabolism, which accumulates in skin layers. The epidermis is made up of stratified squamous epithelium or hardened cells which play a role in the skin's protective function. This is referred to as the stratum corneum. Epidermal cells line the hair follicles, sebaceous glands and sweat glands.

The layers of epidermis are

- Stratum Germinativum (Growing Layer)
- Malpighion Layer (pigment Layer)
- Stratum Spinosum (Prickly cell Layer)
- Stratum Granulosum (Granular Layer)
- Stratum Lucidum
- Stratum Corneum (Horny Layer)

2) Dermis

Non-descriptive region lying in between the epidermis and the subcutaneous fatty region. It consists mainly of the dense network of structural protein fibers, i.e., collagen, reticulum and elastin, embedded in the semi gel matrix of mucopolysaccaridic 'ground substance'. The elasticity of skin is due to the network or gel structure of the cells. Beneath the dermis the fibrous tissue open outs and merges with the fat containing subcutaneous tissue. Dermis thickness ranges from 2000 to 3000 µm and consists of a matrix of connective tissue composed of fibrous proteins.

3) Subcutaneous tissue

This layer consists of sheet of fat rich areolar tissues; know as superficial fascia, attaching the dermis to the underlying structure. Large arteries and vein are present only in the superficial region .The subcutaneous tissue or hypodermis is not actually considered a true part of the structured connective tissue which is composed of loose

textured, white, fibrous connective tissue containing blood and lymph vessels, secretary pores of the sweat gland and cutaneous nerves.

Types of Products for Topical Delivery includes[6]

- External topical that are spread, sprayed or otherwise dispersed on to cutaneous tissues to cover the affected area.
- Internal topical that are applied to the mucous membrane orally, vaginally or on rectal tissues for local activity.

For formulating topical micro-emulgels the challenges to be taken are[5,6]

1. Determining systems that are non-toxic, non-irritating, non-comedogenic and non sensitizing.
2. Formulating cosmetically elegant microemulgel.
3. The microemulgel formulation must have low allergic potential, good physiological compatibility and high biocompatibility.

Advantages of Topical Drug Delivery Systems[6,7,10]

- Convenient and easy to apply.
- Avoidance of first pass metabolism.
- Avoidance of the risks and inconveniences of intravenous therapy and of varied 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 gastro-intestinal incompatibility.
- Providing utilization of drugs with short biological half-life, narrow therapeutic window.
- Improve patient compliance. Provide suitability for self-medication.

Disadvantages of Topical Drug Delivery Systems

- Skin irritation on contact dermatitis may occur due to the drug or excipients.
- Poor permeability of some drugs through the skin.
- Drugs of larger particle size are not easy to absorb through the skin.
- Possibility of allergenic reactions.

Advantages of Using Micro-emulgel As A topical Drug Delivery System[1,3,5,10]

1. Hydrophobic drugs can be easily incorporated into gels using o/w

Microemulsions Most of the hydrophobic drugs cannot be incorporated directly into gel base because solubility act as a barrier and difficulty arises during the release of the drug. Microemulgel helps in the incorporation of hydrophobic drugs into the oil phase and then oily globules are dispersed in aqueous phase resulting in o/w microemulsion. And this microemulsion can be mixed into gel base. This may be proving better stability and release of drug than simply incorporating drugs into gel base.

2. Better stability

Other transdermal formulations are comparatively less stable than micro-emulgels. Like creams shows phase inversion or breaking, powders are hygroscopic and ointment shows rancidity due to oily base.

3. Better loading capacity

Other novel approaches like niosomes and liposome 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 improved loading capacity.

4. Production feasibility and low preparation cost

Preparation of micro-emulgels comprises of easily and short steps which rises the feasibility of the production. There are no specialized instruments needed for the production of micro-emulgels. Moreover materials used are easily available and cheaper. Hence, decreases the production cost of micro-emulgels.

5. No intensive sonication

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

6. Controlled release

Micro-emulgels can be used to prolong the effect of drugs having shorter t1/2. It can be used for both hydrophobic (o/w microemulgel) and hydrophilic drugs (w/o micro-emulsion).

Factors Affecting Topical Absorption of Drug[1,3,6,10]

Physiochemical factors related to drug and physiological factors related to patient that affect the permeation of drug through stratum corneum are listed below

Physiological Factors

a) Skin thickness
b) Lipid content
c) Density of hair follicles
d) Density of sweat glands
e) Skin pH
f) Blood flow
g) Hydration of skin
h) Inflammation of skin Physiochemical Factors
i) Partition coefficient
j) Molecular weight

Physiochemical Factors

a) Partition coefficient
b) Molecular weight (<600 Dalton)
c) Degree of ionization (only unionized drugs gets absorbed well)
d) Effect of vehicles.

Factors to be considered when choosing a topical preparation are[10]

1. Effect of the vehicle e.g. an occlusive vehicle increases penetration of the active ingredient and enhance efficacy. The vehicle itself may have a cooling, drying, emollient, or protective action.
2. Irritation or sensitization potential generally, ointments and w/o creams are less irritating, while gels are irritating. Ointments do not contain preservatives or emulsifiers if allergy to these agents is a concern.
3. Match the type of preparation with the site of application. For example; gel or lotion is typically apply on hairy areas.
4. Match the type of preparation with the type of lesions. For example; avoid greasy ointments for acute weepy dermatitis.
5. The medication should not affect the skin type.

Parts of Micro-emulgel[6,8,12,13]

Micro-emulsion

Gel

Emulsion

Emulsions are biphasic systems in which one immiscible liquid is dispersed into other; due to this the system becomes unstable which is stabilized by emulsifying agents. Emulsion can be either o/w or w/o. These are used as vehicles to deliver drug. Emulsions are stabilized by the use of emulsifying agents. They can be easily washed off from skin and have good penetration capability.

Types of Emulsions

Macro emulsions

These are most common type of emulsions where the particle size of droplets is more than 400nm. They are visually opaque but the individual droplets can be easily observed under microscope. Macro emulsions are thermodynamically unstable, but can be stabilized using surface active agents.

Types of Macro emulsions

These are of two types: o/w and w/o. The type of emulsion formed depends primarily on the nature of emulsifier and on the ratio of components involved and method of emulsification.

Micro Emulsion

Microemulsions are thermodynamically stable, optically transparent, isotropic dispersions of aqueous and hydrocarbon liquids stabilized by an interfacial film of surfactant molecules. The mono dispersed spherical droplets have diameter of 20nm to 200nm.

Double emulsion

Small droplets of one phase are (e.g. oil) dispersed in larger droplets of second phase (e.g. Water) with the latter further dispersed in the former (i.e. oil) as the continuous medium.

GEL

The term gel represents a physical state with properties intermediate between those of solids and liquids. However, it is often wrongly used to describe any fluid system that exhibits some degree of rigidity. A gel consists of a polymer which swells in the presence of fluid and perhaps it within its structure. The rigidity of the gel is determined by the amount of fluid it entraps. These gels are wet and soft and look like a solid material. These are capable of undergoing large deformation in their physical state i.e. from solid to liquid.

Types of micro-emulgel

Macro emulsion gel

These are most common type of micro-emulgel where the particle size of droplets of emulsion is more than 400nm. They are visually opaque but the individual droplets can be easily observed under microscope. Macro emulsions are thermodynamically unstable, but can be stabilized using surface active agents. E.g. Khullar R. et al, mefenamic acid microemulgel was prepared using Carbopol 940 as gelling agent. Liquid paraffin was used as oil phase. Mentha oil and clove oil was used as penetration enhancer. Then it was evaluated for rheological studies, spreading coefficient studies, skin irritation test, in-vitro release, etc.

Nano-emulgel

When nano-emulsion is incorporated into gel it is called as nano-emulgel. Nano-emulsions are thermodynamically stable transparent (translucent) dispersions of oil and water stabilized by an interfacial film of surfactant and co surfactant molecules having a droplet size of less than 100 nm. Nano-emulsion formulations possess improved transdermal and dermal delivery properties in vitro as well as in vivo. Nano-emulsions have improved transdermal permeation of many drugs over the conventional topical formulations such as emulsions and gels. E.g. Singh B. P. et al prepared Carvedilol nano-emulgel using oleic acid and isopropyl myristate (3:1) as oil phase. Tween 20 and Carbitol were used as surfactant and co surfactant respectively. Carbopol 934 was used as gelling agent.

Micro Emulsion gel

Micro emulsions are transparent and thermodynamically stable as their droplet size range from 10 to 100 nm and they do not coalesce. Micro emulsions are composed of oil, surfactant, co surfactant and water in specific proportions. The ingredients of micro emulsion could facilitate the permeation rate of the drug by reducing the diffusion barrier of the stratum corneum. However, due to low viscosity of micro emulsion, their less retention capacity in the skin restrains its application in the pharmaceutical industry. To overcome this disadvantage, gelling agents such as Carbopol 940, xanthan gum and carrageenan have been added into the micro emulsion for forming micro emulsion based gel in order to increase its viscosity which could be suitable for topical application. Moreover, micro emulsion based gel prevents the

absorption of drug in the blood stream and provide higher drug accumulation in the skin for efficient action. E.g. Bachhav Y. G et al, prepared Clotrimazole micro emulsion based vaginal gel using Capryol 90 as oil phase and Cremophor EL as surfactant, Carbopol ETD 2020 is used as gelling agent.

Basic Components of Microemulgel[1,2,6,10]

Microemulgel formulation contains aqueous phase, oils, and emulsifiers for preparation of micro-emulsion as a vehicle, gelling agents for gel preparation and penetration enhancers to increase the flux of drug through skin.

1. Aqueous Material

This forms the aqueous phase of the micro-emulsion. Commonly used agents are water, alcohols.

2. Oils

These agents form the oily phase of the micro-emulsion. For externally applied microemulsions, mineral oils, either alone or combined with soft or hard paraffins, are widely used both as the vehicle for the drug and for their occlusive and sensory characteristics. Widely used oils in oral preparations are non biodegradable mineral and castor oils that provide a local laxative effect, and fish liver oils or various fixed oils of vegetable origin (e.g., Arachis, cottonseed, and maize oils) as nutritional supplements. Some are discussed in table.

Table 1: Uses of Oils.

Chemical	Quantity	Dosage form
Light Liquid Paraffin	7.5%	Emulsion & Microemulgel
Isopropylmyris	7-7.5%	Emulsion
Isopropyl stearate	7-7.5%	Emulsion
Isopropyl palmitate	7-7.5%	Emulsion
Isopropyl palmitate	3-5%	Gel

3. Emulsifiers

Emulsifying agents are used both to promote emulsification at the time of manufacture and to control stability during a shelf life that can vary from days for extemporaneously prepared microemulsions to months or years for commercial preparations e.g. Polyethylene glycol 40 stearate, Sorbitan mono- oleate (Span 80), Polyoxyethylene sorbitan mono-oleate (Tween 80)19, Stearic acid20, Sodium stearate21.

4. Gelling Agents

Gelling agents used to form gel base to incorporate microemulsion in it to prepare microemulgel. Gelling agents are the agents which increase the consistency of any dosage form by swelling in aqueous phase and forming jelly like structure (Bonacucina et al., 2009). They used as thickening agent in microemulgel. The examples of gelling agents are given in table.

Table 2: Uses of Gelling Agents.

Gelling agents	Quantity	Dosage Form
Carbopol-934	1%	Microemulgel
Carbopol-940	1%	Microemulgel
HPMC-2910	2.5%	Microemulgel
HPMC	3.5%	Gel
Sodium CMC	1%	Gel

5. Penetration Enhancers

In order to promote absorption of drugs, vehicles often include penetration enhancing ingredients that temporarily disrupts the skin barrier, fluidize the lipid channels between corneocytes, alter the partitioning of the drug into skin structures, or otherwise enhance delivery into skin. So called penetration enhancers some of these materials given in table.

Table 3: Uses of Penetration Enhancers.

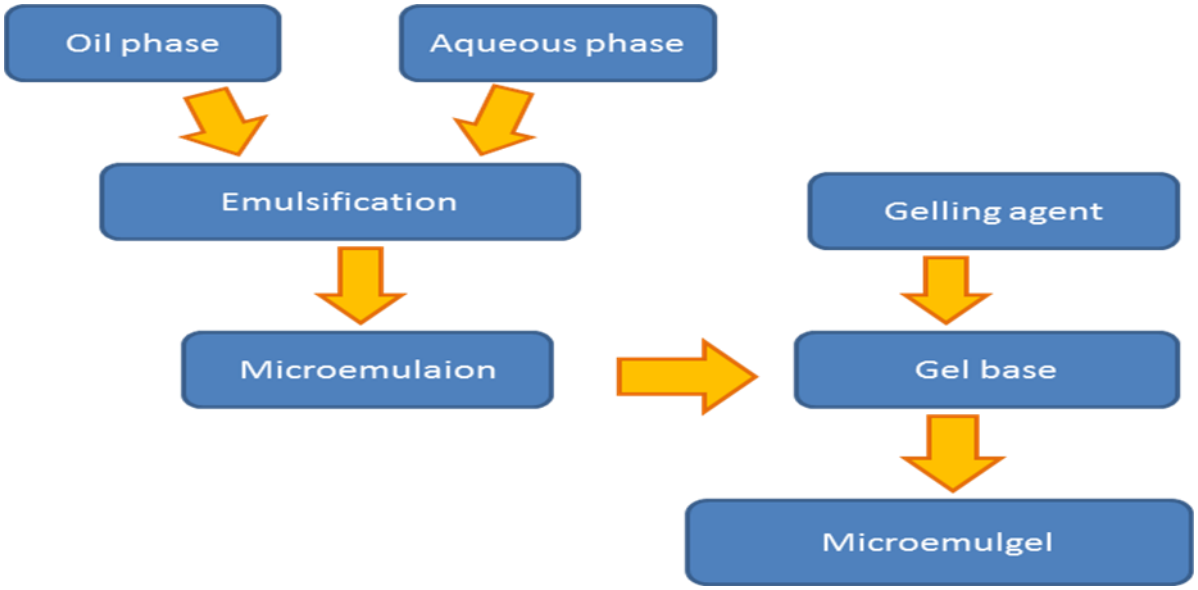
Penetration Enhancer	Quantity	Dosage form
Oleic acid	1%	Gel
Lecithine	5%	Gel
Menthol	5%	Microemulgel
Isopropyl myristate	5%	Gel
Clove oil	8%	Microemulgel

Method of Preparation of Microemulgel

Step 1: Preparation of gel using gelling agent and water by constant stirring and optimization of pH.

Step 2: Preparation of O/W or W/O microemulsion using oil phase and water phase by respected method.

Step 3: incorporation of microemulsion in to gel, Flow diagram showing microemulgel preparation.

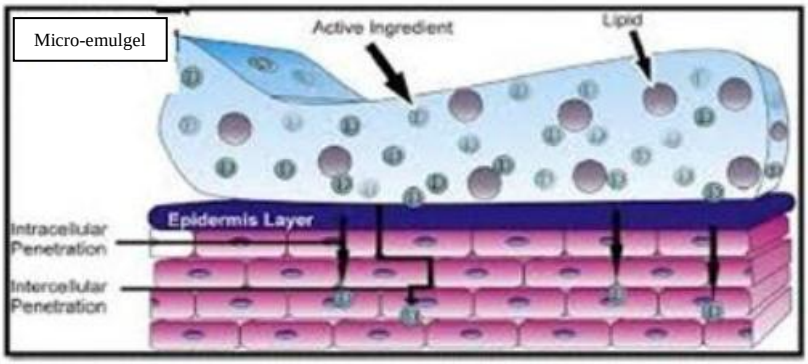


Mechanism of Action of Micro-emulsion[10,11]

A dermally applied micro-emulsion is expected to penetrate the stratum corneum and to exist intact in the whole horny layer alter both lipid and polar pathways. The drug dissolved in the lipid domain of the micro-emulsion can directly penetrate the lipid of the stratum corneum.

The ingredients of micro-emulsion may reduce the diffusion barrier of stratum corneum and increase the permeation rate of drug via skin by acting as permeation enhancers. The hydration effects of micro-emulsion on the stratum corneum may influence the permeation ability of formulations.

Penetration of Microemulgel through Skin



Characterization of Microemulgel[1,4,5,9,10]

1) Physical examination

The prepared microemulgel formulations were examined visually for their colour, appearance, consistency, grittiness, phase separation and homogeneity Consistency, grittiness and phase separation.

2) Rheological study

The viscosity of the formulated batches was determined using a cone and plate viscometer with spindle 62 (Brookfield Engineering Laboratories). The assembly was connected to a thermostatically controlled circulating water bath maintained. The formulation whose Viscosity to be determined was added to a beaker covered with thermostatic jacket. Spindle was allowed to move freely into the microemulgel and the reading was noted.

3) Spreadability

The spreadability of the gel was determined using the following technique:

0.5g gel was placed within a circle of 1 cm diameter pre marked on a glass plate over which a second glass plate was placed. A weight of 1000 g was allowed to rest on the upper glass plate for 5 minutes. The increase in the

diameter due to spreading of the gels was noted. The calculation of spreadability is as follows; S = ML/T

Where,
M = Weight tide to the Upper Slide (g)
L = Length moved on the glass slide (cm)
T = Time taken

4) Skin Irritation Study

The skin irritation test is carried out on male Wistar rats weighing 200 to 225 g. The animals are kept under standard laboratory conditions, with temperature of 25 ± 1°C and relative humidity of 55 ± 5%. The animals are housed in polypropylene cages, six per cage, with free access to standard laboratory diet and water ad li. bitum. The hair on the dorsal side of the rats is removed with an electric hair clipper on the previous day of the experiment. The rats are divided into three groups (n = 6). Group I served as control, without any treatment. Group II receives topical 100-mg selected microemulgel formulation and group III receives 0.8% v/v aqueous solution of formalin as a standard irritant. The animals are applied with new NAP gel, or new formalin solution, each day up to 6 days. Finally, the application sites are graded according to a visual scoring scale, always by the same investigator. The mean erythemal scores are recorded depending on the degree of erythematic. Also Observe like change in colour, change in skin morphology should be checked up to 24 hours. If no irritation occurs the test is passed. If the skin irritation symptom occurs in more than 2 rats the study should be repeated.

5) In vitro drug release study

Franz diffusion cell (with effective diffusion area 3.14 cm^2 and 15.5ml cell volume) is used for the drug release studies. Microemulgel (200mg) is applied on to the surface of egg membrane. The egg membrane is clamped between donor and receptor chamber of diffusion cell. The receptor chamber is filled with freshly prepared PBS (pH 7.4) solution to solubilise the drug. The receptor chamber is stirred by magnetic stirrer. The samples (1.01ml aliquots) are collected at suitable time interval sample are analyzed for drug content by UV visible spectrophotometer at respected wave length after appropriate dilutions. Cumulative corrections are made to obtain the total amount of drug release at each time interval. The cumulative amount of drug release across the egg membrane is determined as a function of time.

6) Measurement of pH

The pH of Microemulgel formulations is determined by using digital pH meter. One gram of gel is dissolved in 100 ml of distilled water and it is placed for two hours. The measurement of pH of each formulation is done in triplicate and average values are calculated.

7) Stability studies

The prepared micro-emulgels were packed in aluminum collapsible tubes (5 g) and subjected to stability studies at 5°C, 25°C/ 60% RH, 30°C/65% RH and 40°C/75% RH for a period of 3 months. Samples were withdrawn at 15-day time intervals and evaluated for physical appearance, pH, rheological properties, drug content and drug release profiles.

8) Compatibility studies by FT-IR

Compatibility study of drug with the excipients was determined by FTIR Spectroscopy. By this we can confirm any chemical interactions between the excipients and the drug.

Marketed Microemulgel Preparations[3,9,10]

DRUG	PRODUCT NAME	MANUFACTURERE
Miconazole nitrate, Hydrocortisone	Miconaz-H-microemulgel	Medical union Pharmaceuticals
Diclofenac diethyl ammonium	Voltarenmicroemulgel	Novartis Pharma
Metronidazole	Lupigyl gel	Lupin Pharma
Clindamycin, Adapalene	Excex gel	Zee laboratories
Benzoyl peroxid	Pernox gel	Cosme Remedies Ltd
Aceclofenac, Methyl salisylate, Capsaicin	Acent gel	Intra labs India Pvt Ltd
Kojic acid, Dipalmitate Arbutin, Octinoxate	Kojivit gel	Micro Gratia Pharma
Clobetasol propionate	Topinate gel	Systopic Pharma
Clindamycin phosphate Allantoin	Clinagel	Stiefel Pharma
Tezarotene	Zorotene gel	Elder Pharmaceuticals
Clotrimazole, Beclomethasone Dipropionate, Neomycin	Cloben gel	Elder Pharmaceuticals
Azithromycin	Avindo gel	Cosme Pharma laboratories

Future scope

In the coming years, topical drug delivery will be used extensively to impart better patient compliance. Since microemulgel possesses an edge in terms of spreadability, adhesion, viscosity and extrusion, they will become a popular drug delivery system. Moreover, they will become a solution for loading hydrophobic drugs in a water soluble gel bases.

CONCLUSION

Microemulgel is one of the best approaches for topical drug delivery of hydrophobic drugs, as microemulgel has several favorable properties Such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, longer shelf life, bio-friendly, transparent & pleasing appearance. Microemulgel have properties of both emulsion and gels

and thus can be used for controlling release rate of drugs with short half-life. Currently, very few marketed microemulgel formulation are available in market however, it offers a vast field for development and research. However, regarding various advantages and future prospective micro-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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