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REVIEW ARTICLE.....!!!

MICROEMULSION BASED GEL: A REVIEW

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ABSTRACT

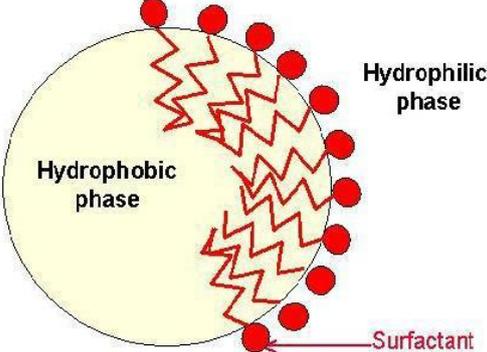
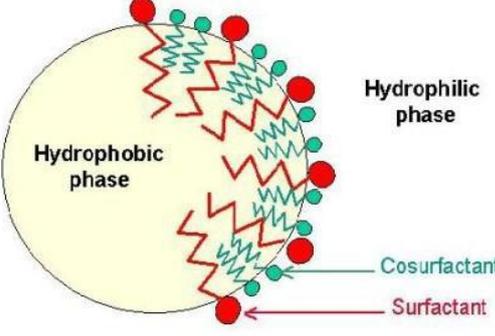
Microemulsions are clear, thermodynamically stable, isotropic mixers of oil, water and surfactant, frequently in combination with co-surfactants, it converted into gel by appropriate gelling agent to form microemulsion based gel. They offer numerous advantages like improved solubilization of both hydrophilic and lipophilic drugs, better bioavailability, prolong and targeted release, enhanced permeation across biological membranes, protection against oxidation, better stability and ease of manufacturing as well as processing. These systems are currently of interest to the pharmaceutical scientist of their unique characteristics and considerable potential to act as drug delivery carrier by incorporating a wide range of drug molecules. In order to appreciate the potential of microemulsion gel as delivery carrier, this review gives an overview of the microemulsion based gel properties, formulation, phase behavior and characterization of microemulsion based gel for drug delivery system.

INTRODUCTION:

Advancements in drug delivery strategies are taking place at much prompt pace than the last decade. Currently 74% of drugs are taken orally but not found to be as effective as desired because of various obstacles coming in path of oral delivery. Now-a-days, transdermal drug delivery system is one of the most capable modes of drug application. Transdermal drug delivery system is the drug delivery via skin to achieve systemic effect of drug. Transdermal application of the drugs offer many advantages as increased patient acceptability, avoidance of gastrointestinal disturbances, bypass of first pass hepatic metabolism¹ and sustained delivery of drugs and reduced systemic side effects². Recent attention has been sharply focused on microemulsions which have additional advantages of stability. Microemulsion represent as novel vehicle having potential of increasing percutaneous delivery of both hydrophilic and lipophilic drugs³ and their use to modify penetration rate of drug across skin.

The word Microemulsion was originally proposed by Hoar and Schulman in the earliest of the 1940s. They were generated a clear single-phase solution by titrating a milky emulsion with hexanol. Microemulsions are thermodynamically stable, isotropically clear mixture of oil, water and surfactant frequently in combination with co-surfactant⁴. These homogeneous systems have gained wide acceptance because of their enhanced drug solubilization, longer shelf life due to thermodynamic stability, easy formation because of zero interfacial tension, ability to be sterilized by filtration⁵. Microemulsion can be considered as small scale version of emulsion i.e. droplet type dispersion. There significant difference between emulsions and miroemulsions. In particular, in emulsions, the average drop size grows continuously with time so that phase separation ultimately occurs under gravitational force, i.e. they are thermodynamically unstable. The drops of the dispersed phase are generally large ($>0.1 \mu\text{m}$) so that they take a milky appearance. On the other side, for microemulsion, spontaneous formation occurs they are clear or translucent in size range of 10-100 nm. Microemulsions are vibrant system in which interface is continuously fluctuating. According to structure they are divided into oil-in-water (o/w), water-in-oil (w/o) and bicontinuous microemulsions. In all these microemulsions interface is stabilized by appropriate combination of surfactant and co-surfactant.⁶

Comparison of microemulsions with emulsions⁷.

Emulsions	Microemulsions
 <p>Surfactant: Forms the interfacial film</p>	 <p>Surfactant: Forms the interfacial film CoSurfactant: Ensures flexibility of interfacial layer => reduces the interfacial tension</p>
Emulsion consists of roughly spherical droplets of one phase dispersed into the other.	They constantly evolve between various structures ranging from droplet like swollen micelles to bicontinuous structure.
Droplet diameter: 1-20 mm	10-100 nm
Most emulsion are opaque (white) because bulk of their droplet is greater than wavelength of light and most oils have higher refractive indices than water.	Microemulsion are transparent or translucent as their droplet diameter are less than $\frac{1}{4}$ of the wavelength of light, they scatter light.
Ordinary emulsion droplets, however small exist as individual entities until coalescence or Ostwald ripening occurs.	Microemulsion droplet may disappear within a fraction of a second whilst another droplet forms spontaneously elsewhere in the system.
They may remain stable for long period of time, will ultimately undergo phase separation on standing to attain a minimum in free energy. They are kinetically stable thermodynamically unstable.	More thermodynamically stable than macroemulsions and can have essentially infinite lifetime assuming no change in composition, temperature and pressure, and do not tend to separate.
They are lyophobic.	They are on the borderline between lyophobic and lyophilic colloids.
Require intense agitation for their formation.	Generally obtained by gentle mixing of ingredients.

In fact, the presence of gelling agent in the water phase converts a microemulsion into microemulsion gel. Both oil-in-water (o/w), water-in-oil (w/o) microemulsions are used as vehicles to deliver various drugs to the skin. Microemulsion gels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, long self life, bio-friendly, transparent and pleasing appearance.

Many widely used topical agents like ointment cream, lotion have many disadvantages. They have very sticky causing uneasiness to patient when applied. Moreover they also have lesser spreading coefficient and need to apply with rubbing. And they exhibit the problem of stability also. Due to all these factors within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations.

A gel is a colloid that is typically 99% wt liquid, which is immobilized by surface tension between it and a macromolecular network of fibers built from a small amount of a gelatin substance present. In spite of many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation an emulsion based approach is being used so that even a hydrophobic therapeutic moiety can be successfully incorporated and delivered through gels⁸.

PHYSIOLOGY OF THE SKIN

The skin has several layers. The outer layer is called epidermis; the layer below epidermis is called dermis. The dermis contains a network of blood vessels, hair follicles, sweat gland & sebaceous gland. Beneath the dermis is a subcutaneous fatty tissue. Bulbs of hair project into these fatty tissues⁹.

The layers of epidermis are:

1. Stratum germinativum (growing layer)
2. Malpighion layer (pigment layer)
3. Stratum spinosum (granular layer)
4. Stratum lucidum
5. Stratum corneum (horny layer).

DRUG PERMEATION THROUGH SKIN

Pathway of transdermal permeation:

1. Transdermal permeation, through the Stratum corneum.
2. Intercellular permeation, through the Stratum corneum.
3. Transappendaged permeation, via the hair follicle, sebaceous and sweat glands.

Skin acts as a major barrier for permeation of any substance into the body and this is mainly due to the stratum corneum, which is its outer layer. In most of its areas, there are 10-30 layers of stacked corneocytes with palms and soles having the most. Each corneocytes is surrounded by a protein envelope and is filled with water-retaining keratin proteins. The cellular shape and orientation of the keratin proteins add strength to the stratum corneum (Fig.1).

When a formulation is applied onto the skin, several gradients are established across it, and drugs, to a certain extent, are able to pass through the stratum corneum. It is also reported that one important factor for drugs to permeate stratum corneum is the water gradient, which can be altered by application of several formulation onto the skin. Hence for effective drug delivery through the skin, an external water gradient could be established. Drugs, when applied onto the skin, can penetrate it via three major routes viz., through sweat glands, stratum corneum or hair follicles (Fig.1).

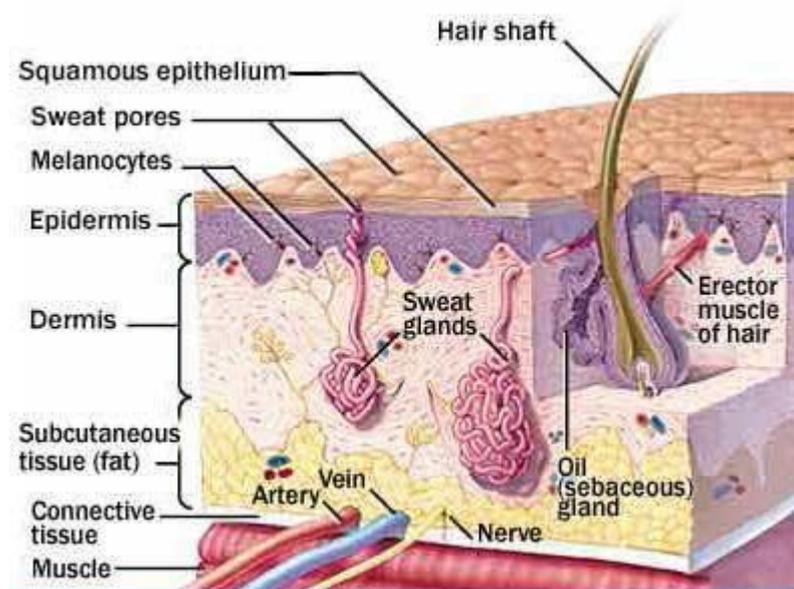


Fig.1 Structure of Skin

There has been a continuous effort for understanding the structural barrier and properties of stratum corneum. The permeation of drugs through hair follicles compared to the stratum corneum is also widely being discussed. Further, it is reported that the follicular route is more favorable for permeation of polar molecules as their influx through the stratum corneum is difficult. There are specific factors which determine efficiency of drug permeation through the skin. The physicochemical nature of drug, site and condition of skin, the formulations, and their influence on the properties of stratum corneum are also important¹⁰.

BASIC PRINCIPLE OF PERMEATION

In the initial transient diffusion stage, drugs molecules may penetrate the skin align the hair follicles or sweat ducts and then be absorbed through the follicular epithelium and sebaceous glands. When a steady state has been reached diffusion through stratum corneum becomes the dominated pathway.

The membrane-limited flux (J) under steady condition is described by expression,

$$J = \frac{DAK_o/w r C}{h}$$

MECHANISM OF DRUG ABSORPTION

Knowledge of skin permeation is vital to the successful development formulation. Permeation of a drug involves the following steps,

Sorption by stratum corneum,

Penetration of drug through viable epidermis, Uptake of the drug by the capillary network in the dermal papillary layer.

This permeation can be possible only if the drug possesses certain physicochemical. The rate of permeation across the skin (dQ/dt) is given by:

$$\frac{dQ}{dt} = P_s (C_d - C_s) \text{-----1.}$$

Where, C_d and C_r are, the concentration of skin penetration in the donor compartment (e.g., on the surface of stratum corneum) and in the receptor compartment (e.g., body) respectively. P_s is the overall permeability coefficient of the skin tissues to the penetrate. This permeability coefficient is given by the relationship:

$$P_s = \frac{K_s D_{ss}}{H_s} \text{-----2.}$$

Where K_s is the partition coefficient for the interfacial partitioning of the penetrate molecular form a solution medium on to the stratum corneum, D_{ss} is the apparent diffusivity for the steady state diffusion of the penetrate molecule through a thickness of skin tissues and H_s is the overall thickness of the skin tissues. As K_s , D_{ss} and H_s are constant under given condition, the permeability coefficient (P_s) for skins penetrate can be considered to be constant.

From equation (1) it is clear that a constant rate of the drug permeation can be obtain when $C_d \gg C_r$ i.e., the drug concentration at the surface of the stratum corneum (C_d) is consistently and substantially greater than the drug concentration in the body (C_r).

The equation (1) becomes:

$$\frac{dQ}{dt} = P_s C_d \text{-----3.}$$

And the rate of skin permeation (dQ/dt) is constant provide the magnitude of C_d remains fairly constant throughout the course of skin permeation. For keeping C_d constant, the drug should be released from the device at a rate (R_r) that is either constant or greater than the rate of skin uptake (R_a) i.e., $R_r \gg R_a$ ¹¹.

FACTOR AFFECTING TOPICAL ABSORPTION OF DRUG**Physiological Factors**

1. Skin thickness.
2. Lipid content.
3. Density of hair follicles
4. Density of sweat glands.
5. Skin pH.
6. Blood flow.
7. Hydration of skin.
8. Inflammation of skin.

Physiochemical Factors

1. Partition coefficient.
2. Molecular weight (<400 Dalton).
3. Degree of ionization (only unionized drugs gets absorbed well)
4. Effect of vehicles

METHOD TO ENHANCE DRUG PENETRATION AND ABSORPTION¹²

1. Chemical enhancement
2. Physical enhancement
3. Biochemical enhancement
4. Super saturation enhancement¹³

ADVANTAGES OF MICROEMULSION GEL^{14,15,16}

1. Hydrophobic drugs can be easily incorporated into gels using microemulsions. Most of the hydrophobic drugs cannot be incorporated directly into gel base because solubility act as a barrier and problem arises during the release of the drug. Microemulsion gel 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. Microemulsion gels apply topically so, avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH and enzymatic activity and drug interaction with food and drinks.
3. To avoid first pass effect, that is, the initial pass of drug substance through the systemic and portal circulation following gastrointestinal absorption, possibly avoiding the deactivation by digestive and liver enzyme.

4. Better stability: microemulsions are thermodynamically stable system; other transdermal preparations are comparatively less stable than microemulsion gels.
5. Microemulsion increase the rate of penetration to the skin barrier so, ultimately increases the rate of absorption and bioavailability.
6. Production feasibility and low preparation cost: Preparation of microemulsion gels comprises of simpler and short steps which increases the feasibility of the production. There are no significant energy and specialized instruments needed for the production of microemulsion gels. Moreover materials used are easily available and cheaper. Hence, decreases the production cost of microemulsion gels.
7. The use of Microemulsion as delivery system can improve the efficacy of a drug, allowing the total dose to be reduced and thus minimizing side effects.
8. 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 microemulsion gels as no sonication is needed.
9. Controlled release: Microemulsion gels can be used to prolong the effect of drugs having shorter $t_{1/2}$.
10. Microemulsion gel is non-invasive and increase patient compliance.
11. Provides protection from hydrolysis and oxidation as drug in oil phase in o/w Microemulsion is not exposed to attack by water and air.
12. Less greasy and can be easily removed from skin.

FORMULATION ASPECTS OF MICROEMULSION GEL

Microemulsions are thermodynamically stable, isotropically clear mixture of oil, water and surfactant frequently in combination with co-surfactant.

1. Oils

Oils are the most essential excipients of microemulsion. Oils solubilize the lipophilic drug in a definite quantity, assist emulsification. A number of natural oils, resulting primarily from plant sources, processed to remove impurities or to separate various fractions of the original product, are available and suitable for use in topical formulation. Naturally occurring oils and fats are mixture of triglycerides, which contains fatty acids of varying chain lengths and degrees of unsaturation. The melting point of particular oil is directly proportional to degree of unsaturation, which also increases the relative susceptibility to oxidation. These might be hydrogenated synthetically to decrease the

degree of unsaturation and conferring resistance to oxidative degradation. Both long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation have been used for the formulation of microemulsion. Modified or hydrolyzed vegetable or edible oils have contributed widely to the success of microemulsion owing to their formulation and physiological advantages. Several semi synthetic liquid and thermo softening (semisolid) excipients, usually prepared by chemically combining medium chain saturated fatty acids or glycerides from natural oils are also used in oral formulations. These excipients are used as a drug solubilizing vehicles, surfactants and wetting agents in microemulsion. Novel semi synthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium- chain triglyceride¹⁷.

2. Surfactants

Various nonionic surfactants such as Tween, labrasol, labrafac CM 10, cremophore etc with high HLB values, can be used in combination with oils to facilitate emulsification. Emulsifiers from natural origin are preferred because of their safety profile compared to synthetic emulsifiers. Nonionic surfactants are known to be less toxic than ionic surfactants. The surfactant chosen must be able to lower the interfacial tension to a very small value which facilitates dispersion process during the preparation of the microemulsion. The general surfactant concentration in microemulsion formulation ranges between 30-60% w/w. Surfactants with high HLB(>12) values assist the immediate formation of O/W droplet and rapid spreading of the formation in aqueous media¹⁸.

3. Co-Surfactants

In most of the cases, single chain surfactants alone are incapable to reduce o/w interfacial tension sufficiently to form microemulsion. Owing to its amphiphilic nature, a co-surfactant accumulates substantially at interface layer, increasing the fluidity of interfacial film by penetrating into surfactant layer. Short to medium chain length alcohols are generally added as co-surfactants helping into increasing the fluidity of interface²¹. Amongst short chain alkanols, ethanol is widely used as permeation enhancer. In medium chain alcohols 1-butanol was reported to be most effective enhancer. The surfactants and co-surfactant ratio is a key factor for phase properties¹⁹.

4. Aqueous Phase

Most commonly, water is used as aqueous phase. The ph of the aqueous phase always needs to be adjusted due to its considerable impact on phase behavior of microemulsion²⁰.

5. Gelling agent

These are the agents used to increase the consistency of any dosage form can also be used as thickening agent.²¹

6. Permeation enhancer

These are agents that partition into and interact with skin constituents to induce a temporary and reversible increase in skin permeability.^{22,23}

METHOD OF PREPARATIONS

1. Phase Titration Method

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. Microemulsions are formed along with various association structures (including emulsions, micelles, lamellar, hexagonal, cubic, and various gels and oily dispersion) depending on the chemical composition and concentration of each component. 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 Fig.(2). 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 metastable systems are not included.

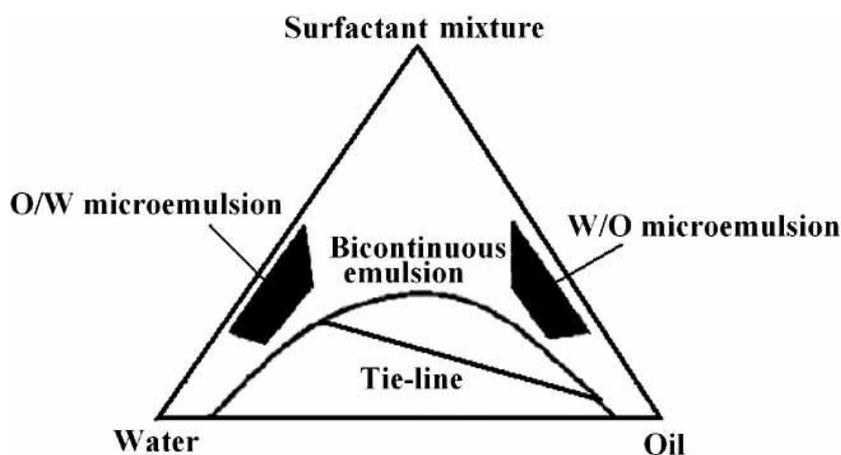


Fig.(2).Pseudo-ternary Phase Diagram of oil, water and surfactant showing Microemulsion region.

2. Phase Inversion Method

Phase inversion of microemulsion occurs upon addition of excess of the dispersed phase or in response to temperature. During phase inversion drastic physical changes occur including changes in particle size that can affect drug release both in vivo and in vitro. These methods make use of changing the spontaneous curvature of the surfactant. For non-ionic surfactants, this can be achieved by changing the temperature of the system, forcing a transition from an o/w microemulsion at low temperature to a w/o microemulsion at high temperature (transitional phase inversion). During cooling, the system crosses a point of zero spontaneous curvature and minimal surface tension,

promoting the formation of finely dispersed oil droplets. This method is referred to as phase inversion temperature (PIT) method. Instead of the temperature, other parameter such as salt concentration or pH value may be considered as well instead of the temperature alone. Additionally, a transition in the spontaneous radius of curvature can be obtained by changing the water volume fraction. By successively adding water into oil, initially water droplets are formed in a continuous oil phase. Increasing the water volume fraction changes the spontaneous curvature of the surfactant from initially stabilizing a w/o microemulsion to an o/w microemulsion at the inversion locus. Short-chain surfactant form flexible monolayers at the o/w interface resulting in a bicontinuous microemulsion at the inversion point²⁴.

CHARACTERIZATION OF MICROEMULSION GEL

1. Physical appearance

The prepared emulsion formulations were inspected visually for their color, homogeneity, consistency and pH. The pH values of 1 % aqueous solutions of the prepared gellified emulsion were measured by a pH meter (Digital pH meter DPH 115 pm).²⁵

2. Spreadability

Spreadability is determined by apparatus suggested by Mutimer et al (1956) which is suitably modified in the laboratory and used for the study. It consists of a wooden block, which is provided by a pulley at one end. By this method spreadability is measured on the basis of 'Slip' and 'drag' characteristics of microemulsion gels. A ground glass slide is fixed on this block. An excess of microemulsion gel (about 2 gm) under study is placed on this ground slide. The microemulsion gel is then sandwiched between this slide and another glass slide having the dimension of fixed ground slide and provided with hook. A 1 Kg weight is placed on the top of the two slides for 5 minute to expel air and to provide a uniform film of the microemulsion gel between the slides. Excess of the microemulsion gel is scrapped off from the edges. The top plate is then subjected to pull of 80 gms. With the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7.5 cm be noted. A shorter interval indicates better spreadability. Spreadability was calculated by using the formula,

$$S = M.L/T$$

Where ,

S = spreadability,

M= weight tied to upper slide,

L = length of glass slides

T = time taken to separate the slides completely from each other.

3. Extrudability²⁶

It is a usual empirical test to measure the force required to extrude the material from tube. The method applied for determination of applied shear in the region of the rheogram corresponding to a shear rate exceeding the yield value and exhibiting consequent plug flow. In the present study, the method adopted for evaluating microemulsion gel formulation for extrudability is based upon the quantity in percentage of microemulsion gel and microemulsion gel extruded from lacquered aluminium collapsible tube on application of weight in grams required to extrude at least 0.5 cm ribbon of microemulsion gel in 10 seconds. More quantity extruded better is extrudability. The measurement of extrudability of each formulation is in triplicate and the average values are presented. The extrudability is then calculated by using the following formula:

$$\text{Extrudability} = \frac{\text{Applied weight to extrude microemulsion gel from tube (in gm)}}{\text{Area (in cm}^2\text{)}}$$

4. Globule size and its distribution in microemulsion gel

Globule size and distribution was determined by Malvern zetasizer. A 1.0 gm sample was dissolved in purified water and agitated to get homogeneous dispersion. Sample was injected to photocell of zeta sizer. Mean globule diameter and distribution was obtained.

5. Rheological Study

The viscosity of the different microemulsion gel formulations is determined at 25°C using a cone and plate viscometer with spindle 52 (Brookfield Engineering laboratories) and connected to a thermostatically controlled circulating water bath.²⁹

6. Swelling Index²⁷

To determine the swelling index of prepared topical microemulsion gel, 1 gm of gel is taken on porous aluminium foil and then placed separately in a 50 ml beaker containing 10 ml 0.1 N NaOH. The samples were removed from beakers at different time intervals and put it on dry place for some time after it reweighed. Swelling index is calculated as follows:

$$\text{Swelling Index (SW) \%} = [(W_t - W_o) / W_o] \times 100$$

Where,

(SW) % = Equilibrium percent swelling

W_o = Original weight of microemulsion gel at zero time

W_t = Weight of Swollen microemulsion gel

7. *Ex-vivo* Bioadhesive strength measurement of topical microemulsion gel.²⁸

(MICE SHAVEN SKIN): The modified method is used for measurement of bioadhesive strength. The fresh skin is cut into pieces and washed with 0.1 N NaOH. Two pieces of skin were tied to the

two glass slide is fixed on the wooden piece and other piece is tied with the balance on right hand side. The right and left pans were balanced by adding extra weight on the left-hand pan. 1 gm of topical microemulsion gel is placed between these two slides containing hairless skin pieces, and extra weight from the left pan is removed to sandwich the two piece of skin and some pressure is applied to remove the presence of air. The balance is kept in this position for 5 minutes. Weight is added slowly at 200 mg/min to the left-hand pan until the patch detached from the skin surface. The weight (gram force) required to detach the microemulsion gel from the skin surface gave the measure of bioadhesive strength. The bioadhesive strength is calculated by using following:

$$\text{Bioadhesive Strength} = \frac{\text{Weight required (in gms)}}{\text{Area(cm}^2\text{)}}$$

8. Drug Content Determination

Drug concentration in gellified emulsion was measured by spectrophotometer . Drug content in Gellified emulsion was measured by dissolving known quantity of Gellified emulsion in solvent(methanol) by sonication . Absorbance was measured after suitable dilution in UV/VIS spectrophotometer (UV-1700 CE, Shimadzu Corporation, Japan)²⁹.

9. In Vitro Release Study

Franz diffusion cell (with effective diffusion area 3.14 cm² and 15.5 ml cell volume) was used for the drug release studies. Gellified emulsion (200 mg) was applied onto the surface of egg membrane evenly. The egg membrane was clamped between the donor and the receptor chamber of diffusion cell. The receptor chamber was filled with freshly prepared PBS (pH 5.5) solution to solubilize the drug. The receptor chamber was stirred by magnetic stirrer. The samples (1.0 ml aliquots) were collected at suitable time interval. Samples were analyzed for drug content by UV visible spectrophotometer after appropriate dilutions. Cumulative corrections were made to obtain the total amount of drug release at each time interval. The cumulative amount of drug released across the egg membrane was determined as a function of time³⁰.

10. Microbiological Assay

Ditch plate technique was used. It is a Technique used for evaluation of bacteriostatic or fungistatic activity of a compound. It is mainly applied for semisolid formulations. Previously prepared sabouraud's agar dried plates were used. Three grams of the gellified emulsion are placed in a ditch cut in the plate. Freshly prepared culture loops are streaked across the agar at a right angle from the ditch to the edge of the plate. After incubation for 18 to 24 hours at 25°C, the fungal growth was observed and the percentage inhibition was measured as follows,

$$\% \text{ Inhibition} = L2/L1 \times 100$$

Where,

L1 = total length of the streaked culture and

L2= length of inhibition.

11. Skin irritation test

A 0.5 gm sample of the test article was then applied to each site (two site per rabbit) by introduction under a double gauze layer to an area of skin approximately 1" × 1" (2.54 × 2.54 cm²). The gellified emulsion are applied on the skin of rabbit. Animals were returned to their cages. After a 24 hour exposure, the gellified emulsion are removed. the test sites were wiped with tap water to remove any remaining test article residue.

12. Accelerated stability studies of gellified emulsion

Stability studies were performed according to ICH guidelines. The formulations were stored in hot air oven at 37 ± 2°, 45 ± 2° and 60 ± 2° for a period of 3 months. The samples were analyzed for drug content every two weeks by UV-Visible spectrophotometer. Stability study was carried out by measuring the change in pH of gel at regular interval of time³¹.

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