Review Article

Microemulsion-based gels: A betterment in topical drug delivery system

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ABSTRACT

Micro emulsions (MEs) are clear, thermodynamically stable, and optically isotropic systems. It is formed by mixing oil, water, surfactant either alone, or combination with cosurfactant, it overcomes limitation of traditional topical formulations to improve topical drug availability, it is also able to increase work of moisturizing agent deeply into the skin. MEs are a drug delivery technology that has emerged as a useful technique for creating safe formulations for insoluble substances while also improving their biopharmaceutical characteristics and pharmacokinetics. This study will explain the current status of microemulsion systems, including an overview of their origins and how they may be correctly generated and extensively characterized using various methods. The examination of stability and toxicity is addressed. A contemporary viewpoint on microemulsion systems finishes the review. Due to their simplicity of manufacture, permeability enhancing activity of its components, and a high solubilizing capacity for diverse pharmaceuticals, MEs have gotten a lot of interest for many applications including cutaneous and transdermal drug administration. Various polymers are now utilized as gelling agents, which serve to minimize the interfacial tension between the oil and aqueous phases of the microemulsion while simultaneously enhancing the viscosity. Transdermal medication delivery provides a number of therapeutic applications on other drug delivery methods. Numerous physical and chemical approaches to circumvent the inherent limited skin permeability have been developed to open the transdermal route for a larger spectrum of medicines, including macromolecules. In this review, various evaluation parameters of MEs are discussed.

Keywords: Microemulsion, Viscosity, Gelling agent, Transdermal drug delivery, Evaluation

Introduction

Topical drug delivery involves the use of a preparation to the epidermis for the treatment of various cutaneous disorders. When oral, sublingual, rectal, or parental routes of pharmaceutical administration fail, or when a local skin ailment, like a fungal infection, the topical drug delivery technique is used. Transdermal medication administration also allows patients to get medicines in a convenient and regulated manner with little pain.[1] However, since the stratum corneum a layer of our skin is the principal resistance to transdermal penetration, microemulsions have the potential to bypass this barrier and increase medication absorption through this route. Microemulsions are also thermodynamically stable isotopically transparent dispersions of two immiscible liquids, such as oil and water, stabilized by an interfacial coating of surfactant molecules having a size range of 5–200 nm and very low interfacial surface tension.[1-3] The fundamental benefit of microemulsions over creams is that they enhance stratum corneum hydration, which increases medication dermal penetration and skin flux. The most significant benefit of microemulsions over creams is that they promote corneum connection, which may boost medication dermal penetration and thereby skin flux.[4] A gel is a liquid combination that is immobilized by a physical phenomena between it and an organic compound network of fibers constructed from a very little quantity of a gelatin-like material present. Gels are a comparatively recent category of indefinite quantity type generated by denying massive volumes of binary chemical or hydro alcoholic liquid in a dense network of mixed solid particles.

When opposed to ointments and lotions, gel formulations often have a faster drug hardness. Despite their numerous benefits, gels have a fundamental drawback; they are unable to deliver hydrophobic medicines. Because a water insoluble medication cannot be directly

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integrated into a gel base system, microemulsions have the benefit of being able to solubilize pharmaceuticals and enhance topical drug availability. Because they include both a gel and a microemulsion control mechanism, microemulsion-based gels have evolved as one of the most exciting topical drug delivery technologies. Due to it's a dual management platform, namely, gel and microemulsion, microemulsion-based gels have emerged as one of the most exciting topical drug delivery technologies. The microemulsion-based gel for dermatologic use has various benefits, including thixotropic, greaseless, readily spreadable, easily washable, emollient, non-staining, soluble, extended time period, bio-friendly, transportable, and appealing look. Microemulsions have received a lot of interest for their ability to deliver hydrophobic drugs for both general and native therapy.[5] Microemulsions may be exploited as possible drug delivery methods due to their unique solubilization capabilities, either as topical carriers or as bioavailability enhancers for active pharmacological components that are poorly water soluble (API). An emulsion-based approach is being used to effectively integrate and distribute a hydrophobic medicinal component through gels to circumvent this restriction.[6]

Evaluation Parameters of Microemulsion (ME)-based Gel System

Microemulsion-based gel system was evaluated for Rheological studies, globule size, extrudability study, drug content determination, spread ability, skin irritation test, microbiological assay, *in vitro* release perform study, pH determination, optical transparency, stability, particle droplet size, refractive index, polydispersity index, photo degradation test, dilution test, and swelling study.

Rheological Studies

The viscosity of several microemulsion-based gel compositions is tested at 25°C with a cone and plate viscometer, spindle 52 associated to a thermostatically controlled mixing water bath.[7,8] The rheological features of emulsion-filled gels are principally determined by the gelled continuous phase. An oil-in-water emulsion exhibits viscoelastic behavior when its continuous phase is created by a viscoelastic biopolymer solution or gel, according to Dickinson. The presence of dispersed filler particles, on the other hand, has a significant impact on the textural features of gelled systems such as emulsion-filled gels [Figure 1].

Extrudability Study of Topical Microemulsion-Based Gel

The force needed to extrude the material from the tube is typically measured using an empirical test. The method used to assess the extrudability of microemulsion-based gel formulations is based on the number of shares of gel and gel made from an Al tip-up tube, as well as the weight in grams needed to extrude a minimum of 0.5 cm ribbon of microemulsion-based gel in 10 s. Extrudability is the ability to extrude a large volume of material. Every formulation's extrudability activity is done in triplicate; hence, the average results are given.[9] The extrudability is then computed using the following formula:

$$Extrudability = \frac{Applied\ weight\ to\ extrude\ microemulsion\ based\ gel\ \ from\ the\ tube}{Area}$$

Drug Content Determination

Mix 1 g of gel based on microemulsion in a solvent. Strain the solution to get a clear result. obtain its absorbance using a UV-visible spectrophotometer. A conventional drug plot may be made in the same solvent. Concentration and drug content may be calculated by plotting the value of absorbance[10] on the same standard plot.

Spread ability

The spreading coefficient of the formulations was evaluated using an apparatus described by consisting of two glass slides (7.5 × 2.5 cm), one of was fixed to the picket board and the other of which was moveable, linked to a thread that skipped over a simple machine bearing a weight. Between the two glass slides, 1 g of formulation was inserted. To remove entrapped air between the slides and create a uniform coating of the formulation, the weight (100 g) was allowed to lie on the top slide for 1–2 min. The weight was removed, and a pull was applied to the top slide by placing a 30 g weight over the pulley. The time it took for a moving slide to move a premarket distance of 6.5cm (in seconds) was recorded and reported as spread ability.[11] The following formula is used to determine spread ability:

$$S = \frac{M \times L}{T}$$

Where,
M = weight tied to upper slide
L = length of glass slides
T = time taken to separate the slide.

Skin irritation test

The skin irritation investigation taken out with the agreement of the Animal Ethical Committee, and test animals were white male rabbits (n = 3). The hair on the dorsal side of the rabbits was shaved

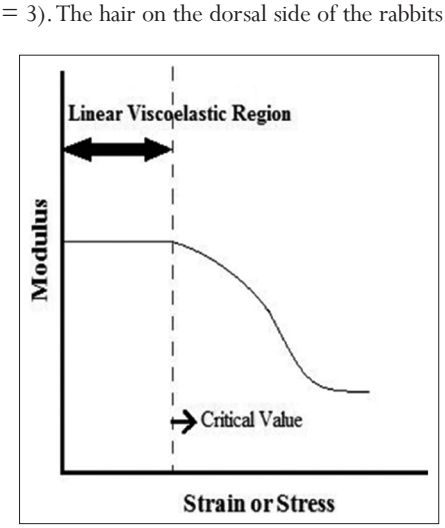

Figure 1: Rheological study strain and stress

using an electrical shaver, and a 4 gm sample of the test product was then administered to each site (two per rabbit) by introducing it beneath a double gauze layer to an area of skin measuring 1″ × 1″ (2.54 × 2.54 cm^2). The gellified emulsion is applied to rabbits' skin. The animals were escorted back to their enclosures. The gellified emulsion is removed after a 24-h exposure. To remove any remaining gel, the examination locations were cleaned with water. Visual observation was used to track the progression of erythema/edema for 3 days.[12]

Microbiological assay

The skin irritation investigation was taken out with the agreement of the Animal Ethical Committee, and test animals were white male rabbits ($n = 3$). The hair on the dorsal side of the rabbits was shaved using an electrical shaver, and a 4 g sample of the test product was then administered to each site (two per rabbit) by introducing it beneath a double gauze layer to an area of skin measuring 1″ × 1″ (2.54 × 2.54 cm^2). The gellified emulsion is applied to rabbits' skin. The animals were escorted back to their enclosures. The gellified emulsion is removed after a 24-h exposure. To remove any remaining gel, the examination locations were cleaned with water. Visual observation was used to track the progression of erythema/edema for 3 days.[12,13]

In vitro release/permeation studies

To analyze the impact of the formulation parameters, the *in vitro* permeation rates of produced microemulsion-based gels were evaluated. Diffusion tests were carried at 37 0.1°C with Franz diffusion cells built locally with a dialysis membrane pore size of 0.2 mm. The receptor fluid was 200 mL of phosphate buffer pH 7.4 in the beaker. Externally powered magnetic beads were continually stirring the receptor fluid. 1 g of microemulsion-based gel was accurately put in a cylindrical hollow tube with one end sealed by a dialysis membrane with a pore size of 0.2 mm. It serves as a donation container. The aliquots were taken at 30-min intervals up to 6 h intervals. After each sample, an equivalent amount of new phosphate buffer was immediately refilled. After proper dilutions with sufficient solvent, the sample was evaluated by UV-visible photometer at an acceptable wavelength. To determine the overall quantity of medication released at each time period, cumulative adjustments were done.[12]

pH determination

A 10% dispersion of the formulation in distilled water was made, and the pH was evaluated using a pH meter that had been previously calibrated with standard buffers of pH 4 and pH 7.[12]

Optical transparency

Inspection of the sample in clear and clear instrumentality in the presence of great lightweight against reflection into the eyes, and seen against a black and white well-lit backdrop resolves the formulation's optical transparency.[13]

Stability

The stability of microemulsion base gel is studied by following methods.

Centrifugation**:** The chosen formulations were centrifuged for 30 min at 3000 rpm. For the heating and cooling cycle, we used formulas with no section separations (freeze thaw cycle). Six cycles were performed using a hot air kitchen appliance at temperatures ranging from 4°C (refrigerator) to 45°C, with storage at each temperature for no more than 48 h. For further research, the formulations that were stable at these temperatures were chosen.[14]

This is utilized to determine whether or not the microemulsion is monophasic in nature. The samples were spun for 30 min at 10,000 rpm in a cold centrifuge to determine if the system was monophasic or biphasic.[15]

Mechanical stress study

Mechanical stress testing was used to obtain the chemical and physical compatibility of microemulsions. The three microemulsion formulations (ME-1 to ME-5) were centrifuged at 2000 rpm for varied time intervals (10, 30, and 60 min) and the volume of phase separation of the formulation was recorded.[15]

Analyzing transmission profile

The transmission profiles (T) acquired by multiple light scattering utilizing the turbi scan laboratory equipment, whose light source is near-infrared (= 880 nm), were used to assess the physical stability of the microemulsion base gel. The turbi Scan laboratory is a characterization tool for emulsions and dispersions that use the measure of disperse (BS) and transmission (T) signals to detect destabilizing processes such as driblet aggregation and migration early on.[16]

Freeze thawing

The stability of the microemulsion formulations was tested using freeze thawing. The ME preconcentrates of different formulations were frozen for 24 h at −10°C and then thawed for 24 h at 40°C. After that, the various formulations were exposed to 5 min of activity at 3000 revs. After that, the formulations were visually examined for phase separation.[17]

Particle/droplet size

The following methodologies/equipment are used to determine particle size:

A microparticle size analyzer is a device that measures the size of microparticles. At 25°C, the average driblet size of the ready microemulsions was measured 3 times. maltreatment Quidix Particle size analyzer for micro particles (Scatter scope I model, Quidix Inc., South Korea).[17]

Malvern Zetasizer

A Malvern Zetasizer (Worcestershire, UK) fitted with 200 Hydro MU was used to quantify the common driblet size of the microemulsion samples at 25°C. Using a plastic syringe or micropipette, the microemulsion and

drug (sample) microemulsion-loaded hydrogel (2.74 g) were moved to a polystyrene cuvette, and the droplet size of the microemulsion was assessed and estimated based on the volume size distribution.[18]

Dynamic Light Scattering (DLS)

At 20°C and 32°C, a nano ZS, Malvern equipment was used to evaluate the hydrodynamic radius and polydispersity of the ME structures using DLS. Five minutes before measurement, ME samples were controlled.

DLS was used to define the mean thickness of the microemulsion oil droplets at 25.0 0.1°C using a 90 Plus Particle Size Analyzer. Microemulsions were suitably diluted in water before to measurement, and hence, the findings were derived straight from device information fitting through the inverse "Laplace transformation," and thus the Contin methods.[19]

Transmission Electron Microscopy (TEM)

The formulation was TEM examined using a JEOL JEM-1010 microscope to confirm droplet size (JEOL Ltd., Tokyo, Japan). A drop of undiluted ME put on a formvar coated copper network for 1 min for negative staining. The grid was cleaned with a drop of ultrapure water after blotting the excess formulation. The sample was then stained for 1 min with uranyl acetate®. After 24 h of drying, TEM images were obtained.

The structure of the microemulsion was investigated using a Topcon 002B transmission electron microscope with a 200kv working voltage and point-to-point resolution (Topcon, Paramus, NJ). A drop of the microemulsion was diluted with water and placed to a carbon-coated grid for TEM observations, after which it was treated with a drop of 2% phosphotungstic acid and left for 30 s. The coated grid was vacuum-dried before being placed on a grid holder and examined using a TEM.[20]

Atomic Force Microscopy (AFM)

Visualizing particles with sizes ranging from 1 nm to 10 m with an AFM are a breeze. Another advantage of the AFM is its ease of use, as it requires the least amount of sample preparation.

The AFM produces three-dimensional profiles in comparison to traditional techniques for single particle analysis of sub-m particles. With an AFM, it is possible to make quantitative measurements of particle sizes. It will simply maintain particle size parameters as long as the particle is larger than 100 nanometers. If the particle size is less than one hundred nanometers, special considerations should be made.[21]

Laser Particle Counting Method

The optical maser particle investigating methodology was used to evaluate the microemulsion formulations. The sample was injected into the dominant chamber and sample delivery chamber. The chamber was then wired with the appropriate solvent. A beam of optical maser light is now being permitted to fall on the sample cell. They were directed toward the detector once the required range of runs had been reached. The particle size varies, thus, the mean particle size of the formulation is often examined. Microemulsion formulations' common particle size is frequently determined using a particle size instrument.[22]

Electron Paramagnetic Resonance Measurements

At room temperature, electron paramagnetic resonance measurements were made with a Bruker EMX EPR spectrometer in the X-band, and the CW spectra were accumulated with Bruker Win EPR Acquisition Software.[22]

Refractive index

By depositing drop of ME on slide, the refractive index of MEs was checked using an Abbe refract meter (Bausch and Lomb, New York, USA).[23]

Isotropic study

The MEs' isotropic nature was confirmed by putting a drop on a glass slide with a cover glass over it that was detected in cross-polarized light using a polarizing magnifier (Carl Zeiss, Germany).[23]

Electric conductivity

The conductivity of an optimized microemulsion base gel formulation was measured to determine the continuous phase in the microemulsion, and the flow of current was recorded using a conductivity meter (Laboratory India, PICO or CM-180 ELICO, India).[24]

Photo Degradation Test

All of the prepared emulgel formulations were subjected to photo degradation tests under the following conditions: corresponding to 21 kJ/m^2 min, temperature 25°C irradiation power 350 W/m^2. By UV radiation spectrophotometry, the samples were evaluated simply when prepared (t = 0 min) and at a variety of disclosure durations (10, 30, 50, up to 300 min). To reduce additive light interferences, all laboratory trials were conducted in a dark room.[25]

Dilution Test

To find if the system has any signs of separation, the microemulsions diluted in 1:10 and 1:100 ratios with double distilled water. To confirm the type of emulsion and miscibility with the aqueous phase, the formulated microemulsions were diluted with distilled water.[26]

Swelling Index

The quantity of swelling was calculated using the percentage weight obtained by the hydrogel mass. In a Petri dish with 10 mL of buffer solution, 1 g of each hydrogel formulation weighed and stored on a

sieve at pH 5.8. Conclusion of the time intervals, the hydrogel-holding sieve was withdrawn from the Petri dish, and the excess buffer was soaked in tissue paper and weighed.[27] The proportion of weight acquired by the hydrogel calculated with equation.

Where,

$$Swelling\ index(\%) = \frac{(Mt - Mo)}{Mo} \times 100$$

Mt = weight of the sildenafil ME, *t*-formulation of Loaded hydrogel at a time *M0* = initial weight of the hydrogel formulation.

Advantages of Using ME-Based Gel as Topical Drug Delivery System

Most lipophilic medicine unable to be mixed into the base of gel due to solubility which has a role as a barrier, which causes a difficulty during drug release.[28] Microemulsion-based gels aid in the incorporation of lipophilic medicine into the oil section by distributing oily globules in a binary compound section, resulting in (o/w) microemulsion, which is then mixed into the gel base.[29] This may provide greater drug stability and release than simply incorporating medicine into a gel base. Low cost, loading capacity, feasibility in production and better stability, no sonication, and controlled release: ME-based gels will be used to extend the impact of medicines with shorter half-lives.[30]

Conclusion

MEs-based gel system have proven as most convenient, better, and effective topical delivery system. Due to its non-greasy gel like property and lacks of oily bases, it provides a better release of drugs as compared to other topical drug delivery system. The microemulsion-based gels were evaluated for physical characterizations pH, appearance, spread ability, extractability, and viscosity separation, creaming associated with microemulsion.

References

1. Sharadha M, Gowda DV, Gupta V, Akhila AR. An overview on topical drug delivery system – Updated review. Int J Res Pharm Sci 2020;11:368-85.
2. Patel V, Kukadiya H, Mashru R, Surti N, Mandal S. Development of microemulsion for solubility enhancement of clopidogrel. Iran J Pharm Res 2010;9:327-34.
3. Singh V, Bushettii SS, Raju AS, Ahmad R, Singh M, Bisht A. Microemulsions as promising delivery systems: A review. Indian J Pharm Educ Res 2011;45:392-401.
4. Chandra A, Sharma PK. Microemulsions: An overview. Pharm Rev 2008;6:2-4.
5. Zhu W, Guo C, Yu A, Gao Y, Cao F, Zhai G. Microemulsion-based hydrogel formulation of penciclovir for topical delivery. Int J Pharm 2009;378:152-8.
6. Kawakami K, Yoshikawa T, Moroto Y, Kanaoka E, Takahashi K, Nishihara Y, *et al*. Microemulsion formulation for enhanced absorption of poorly soluble drugs. I. Prescription design. J Control Release 2002;81:65-74.
7. Shahin M, Hady SA, Hammad M, Mortada N. Novel jojoba oil-based emulsion gel formulations for clotrimazole delivery. AAPS PharmSciTech 2011;12:239-47.
8. Bhatt P, Gnanaranjan G. Emulgel: A novel formulation approach for topical delivery of hydrophobic drugs. Int Res J Pharm 2013;4:12-6.
9. Gupta M, Verma PR, Marwaha RK, Faruk A, Singh G. Formulation and evaluation of meloxicam gel. J Pharm Res 2008;7:27-31.
10. Sandeep G, Vasavi RD, Devireddy SR. Formulation and evaluation of fluconazole pro-niosomal gel for topical administration. J Appl Pharm Sci 2014;4:98.
11. Jones DS, Woolfson AD, Brown AF. Textural, viscoelastic and mucoadhesive properties of pharmaceutical gels composed of cellulose polymers. Int J Pharm 1997;151:223-33.
12. Masmoudi H, Piccerelle P, Le Dréau Y, Kister J. A rheological method to evaluate the physical stability of highly viscous pharmaceutical oil-in-water emulsions. Pharm Res 2006;23:1937-47.
13. Saleem MA, Sanaullah S, Faizan S. Formulation and evaluation of gatifloxacin topical gels. Indian Pharm 2006;5:88-92.
14. Ravikumar P, Tatke P. Design of an encapsulated topical formulation for chemoprevention of skin cancer. Int J Pharm Sci Res 2019;10:309-19.
15. Aulton ME. Pharmaceutics the Science of Dosage Form Design. 2nd ed., Vol. 41. New York: Charchil Livingstone; 1988. p. 355-6.
16. Kantarci G, Ozgüney I, Karasulu HY, Arzik S, Güneri T. Comparison of different water/oil microemulsions containing diclofenac sodium: Preparation, characterization, release rate, and skin irritation studies. AAPS PharmSciTech 2007;8:E91.
17. Bajpai M, Sharma PK, Mittal A. A study of oleic acid oily base for the tropical delivery of dexamethasone microemulsion formulations. Asian J Pharm 2014;3:208-14.
18. Ahlneck C, Zografi G. The molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state. Int J Pharm 1990;62:87-95.
19. Shah V, Bharatiya B, Shah DO, Mukherjee T. Correlation of dynamic surface tension with sedimentation of PTFE particles and water penetration in powders. Langmuir 2015;31:13725-33.
20. Hsu JP, Nacu A. Behavior of soybean oil-in-water emulsion stabilized by nonionic surfactant. J Colloid Interface Sci 2003;259:374-81.
21. Goffredi M, Liveri VT, Vassallo G. Refractive index of water-AOT-*n*-heptane microemulsions. J Solut Chem 1993;22:941-9.
22. Aboofazeli R, Lawrence MJ. Investigations into the formation and characterization of phospholipid microemulsions. I. Pseudo-ternary phase diagrams of systems containing water-lecithin-alcohol-isopropyl myristate. Int J Pharm 1993;93:161-75.
23. Eicke HF, Borkovec M, Das-Gupta B. Conductivity of water-in-oil microemulsions: A quantitative charge fluctuation model. J Phys Chem 1989;93:314-7.
24. Kotlarchyk M, Stephens RB, Huang JS. Study of Schultz distribution to model polydispersity of microemulsion droplets. J Phys Chem 1988;92:1533-8.
25. Jones CE, Mackay RA. Reactions in microemulsions. 3. Photodegredation of chlorophyll. J Phys Chem 1978;82:63-5.
26. Vicentini FT, Vaz MM, Fonseca YM, Bentley MV, Fonseca MJ. Characterization and stability study of a water-in-oil microemulsion incorporating quercetin. Drug Dev Ind Pharm 2011;37:47-55.
27. Bartoň J, Stillhammerová M. Inverse microemulsion polymerization of acrylamide in the presence of hexamethylenetetramine. Macromol Chem Phys 1996;197:1093-100.
28. Date AA, Nagarsenker MS. Parenteral microemulsions: an overview. Int J Pharm 2008;355:19-30.
29. Kogan A, Garti N. Microemulsions as transdermal drug delivery vehicles. Adv Colloid Interface Sci 2006;123-126:369-85.
30. Schwuger MJ, Stickdorn K, Schomaecker R. Microemulsions in technical processes. Chem Rev 1995;95:849-64.