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OVERVIEW OF MICROEMULSION-BASED GELS: A COMPREHENSIVE REVIEW OF RECENT RESEARCH AND APPLICATIONS

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ABSTRACT

Microemulsions are transparent, thermodynamically stable colloidal systems. Over the recent years, they have been increasingly investigated due to their potential as skin delivery vehicles for a wide range of drug molecules. It can able to incorporate hydrophobic drugs, butdue to low viscosity of microemulsion it is unable to easily spread on the skin, hard to handle. On the other hand, gels provide sufficient viscosity for application of topical use. Clinical evidence indicates that topical gel is a safe and most effective treatment option for use in the management of skin related disease and used for local actions. But gels have limitation of inability to incorporate hydrophobic drugs. Low water soluble/water insoluble drug can be delivered through transdermal route by fabricating the microemulsion into gel system. This article discuses about formulation and characterization of microemulsion based gel and recent research work that formulate drug in the microemulsion based gel system.

KEYWORD: Microemulsion based gel, topical drug delivery of hydrophilic drug, microemulsion.

INTRODUCTION

Topical drug delivery is a system for delivering drugs locally to any site in the body through ophthalmic, rectal, vaginal, and dermal routes. The drug formulation can be applied to the skin to directly treat skin disorders.[1] Main advantage of topical drug delivery systems is that they have the ability to deliver drugs more selectively to a specific site. They allow use of drugs with short biological half-lives and narrow therapeutic windows to increase the duration of action.[2]

Topical drug delivery systems have many advantages over oral routes, such as high absorption rates, avoidance of first-pass metabolism, and ease of use, making them an advantageous delivery system over conventional drug delivery systems.[3] Many of the widely used topical agents such as ointments, creams and lotions have some disadvantages. They cause discomfort to the patient during application due to their sticky nature and have to be applied by rubbing as they have a lower spreading coefficient. They also present stability problems. Due to these limitations, the use of transparent gels in pharmaceutical preparations is increasing.[4] Clinical evidence indicates that topical gel is a safe and most effective treatment option for use in the management of skin related disease and used for local actions.[5] Gels may prove to be a useful vehicle for local drug delivery or local drug action on the skin, such as in sprains or acute musculoskeletal disorders.

Gels are defined as semi-solid formulations, containing an external solvent phase, which are hydrophobic or hydrophilic in nature and are fixed within the available spaces of a three-dimensional network structure. Gels are unique materials that are both rigid and elastic and have a wide range of applications in cosmetics, medicine, biomaterials and food technology.[6]

Despite these advantages, the main limitation of gels is their inability to incorporate hydrophobic drugs. Water-insoluble drugs cannot be incorporated directly into gel systems, hence microemulsion-based approaches are used to successfully incorporate drugs into gel-based systems. When microemulsions and gels are used in combination to form microemulsion based gel, they exhibit properties of both. Microemulsions help deliver hydrophobic drugs by forming oil-in-water microemulsions that can be incorporated into the gel matrix. They provide a larger surface area for drug absorption and the lipid fraction enhances bioavailability due to better drug permeability. In addition, the gel layer also provides better stability to the microemulsion. In

addition, the gel layer also provides better stability to the microemulsion.[7]

Microemulsionbased gels

The microemulsion concept was introduced as early as the 1940s by Hoar and Schulman.[8] Microemulsion, a colloidal system, is an important delivery vehicle for lipophilic and hydrophilic drugs because of its unique properties, such as its transparent, optically isotropic, thermodynamically stable nano-sized droplets and permeation because of its very low surface tension.

Microemulsion refers to a well-defined, thermodynamically stable system formed by self-assembly of an oil phase, an aqueous phase, a surfactant, and a co-surfactant. The microemulsion has a droplet size between 10 to 100 nm and is evenly distributed.[9]

Physiological barrier of the skin, especially the stratum corneum, is a major limitation in the development of transdermal formulations for drug delivery. The stratum corneum is composed of highly dense lipids that reduce or even impede drug penetration. Most drugs cross the barrier with very low flux; thus, it is difficult to achieve effective therapeutic concentrations. In recent years, microemulsions have been widely used in transdermal drug delivery due to their remarkable permeation-promoting effects.[10]

Microemulsions have several advantages for topical and transdermal formulations, including improved skin delivery by increasing the solubility of hydrophilic and lipophilic molecules and improved skin penetration rates. However, the high fluidity of microemulsions limits their transdermal application due to impractical use. Several gelling agents such as Carbomer 940, xanthan gum, and carrageenan have been used to modify the rheological properties of microemulsions. Stable microemulsion-based hydrogels have good penetration and suitable viscosity when applied topically, allowing for longer contact with the skin.[11]

Considering the nature of the droplets, microemulsion systems can be divided into water-in-oil (w/o) and oil-in-water (o/w) types, or bicontinuous (BC) structures, in which the two phases coexist with none of them form separate spherical droplets.[12]

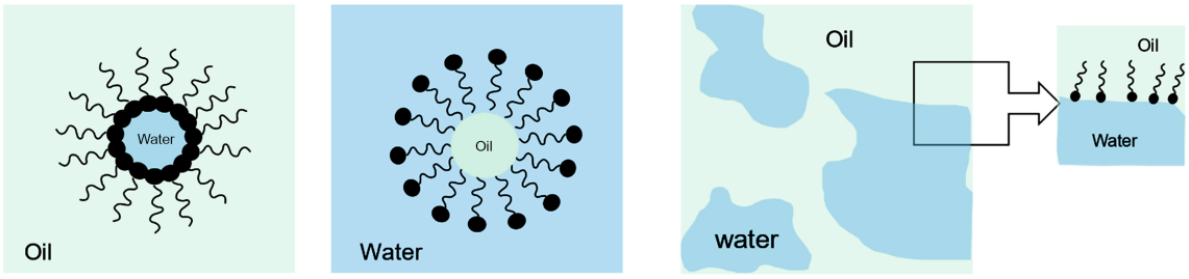

Figure 1: Microstructures of the microemulsion.

(A. Water in oil microemulsion, B. Oil in water microemulsion, C. Bicontineous microemulsion).[13]

Studies have found that microemulsions can emulsify sebum and other lipids in skin tissue, thereby increasing drug penetration into the stratum corneum.[14] Microemulsion gels have strong moisturizing ability, regulate drug release, and promote drug retention in the skin.[15] Many studies have confirmed that the drug release behaviour from microemulsion gels follows Higuchi's zero-order, first-order, and third-order kinetic equations.[13]

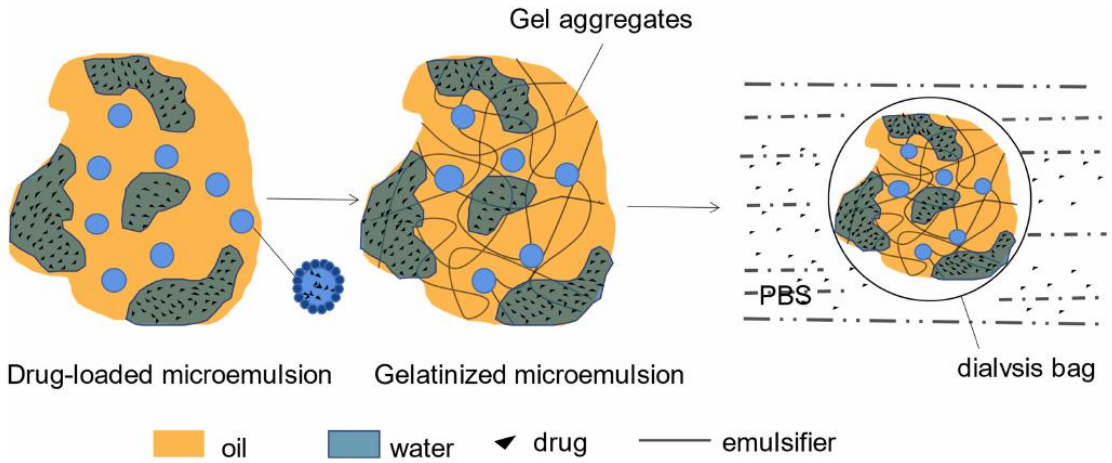

Figure: 2 Release of drug from the gelled microemulsions.

Advantages of microemulsion based system

Microemulsions exhibit several advantages as a drug delivery system

1) High loading capacity
   Compared with other novel approaches such as liposomes and niosomes, gels have relatively larger drug loading capacity due to their large network.
2) Production feasibility
   Production of microemulsion-based gel is carried out in short and simple steps, this increases the feasibility of the preparation also in the preparation of microemulsion-based gels, no specialized instruments needed for the production.
3) Ability of incorporation of hydrophobic drugs
   Major problem of incorporating most of the hydrophobic drugs (mainly Biopharmaceutical class II drugs) directly into the gel base is solubility. Microemulsion-based gel helps to avoid this constraint. Microemulsion-based gel incorporates these lipophilic drugs into the oil phase and then oily globules are dispersed in an aqueous phase bringing about o/w emulsion. Instances of such drugs are ketoconazole, fluconazole, and so on.
4) No intensive sonication
   Intensive sonication is needed in the preparation of vesicular molecules which may result in leakage and drug degradation. But this problem is not encountered during the preparation of microemulsion-based gel as sonication is not required.
5) Avoids first pass effect
   Concentration of drugs are reduced as the drug substance move through the portal circulation following gastrointestinal absorption. The deactivation of the drug by digestive and liver enzymes can be avoided by the use of microemulsion-based gels.
6) Controlled release

The effect of drugs having shorter half-lives can be prolonged by the use of microemulsion based gel.[16]

Disadvantages of microemulsion based system

1) Require large amount of surfactant/co-surfactant for stabilizing droplets.
2) Surfactant should be nontoxic for use in pharmaceutical applications.
3) Microemulsion stability is influenced by environmental parameters such as temperature and pH.[17]

Formulation of microemulsion based gels

To formulatemicroemulsion based gel, microemulsion is first formulated and then the microemulsion is introduced into the gel system.

Preparation of microemulsion

Major component in microemulsion system is-

1) Oil phase
2) Surfactant (primary surfactant)
3) Co-surfactant (secondary surfactant)
4) Co-solvent

Firstly, a suitable oil phase, surfactant, and co-surfactant should be selected. A solubility of the drug in various oils, surfactants, and co-surfactants is performed to identify suitable excipients. Saturation solubility of the drug in various oils, surfactants, and co-surfactants is evaluated.[18]

Selection of surfactants

Selection of an appropriate surfactant for the preparation of microemulsions is important. Generally, non-ionic surfactants are preferred in dermal pharmaceutical applications due to concerns about the toxicity of ionic surfactants. Non-ionic surfactants are not affected by changes in pH in the body environment.

To promote solubilization and stability of microemulsion system, a blend of hydrophobic and hydrophilic surfactant is used to adjust HLB to the oil phase HLB and decrease the interfacial tension between oil and aqueous phase.[19]

Construction of pseudo ternary phase diagram

To determine appropriate surfactant mixture and concentration range of microemulsion components, pseudo-ternary phase diagram is constructed using water titration method for various surfactant ratios at ambient temperature.[20] Pseudo-ternary phase diagrams are constructed by water titration at room temperature (25°C) using the ternary phase diagram software tools (e.g. CHEMIX-Ternary diagrams software). Different ratiosof surfactant and co-surfactant (Smix) are used to construct pseudo-ternary phase diagrams. For each phase diagram, the oil and Smix ratios are mixed as follows: 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8 :2, 9:1 (% w/w). Then, water is added dropwise to each oil-Smix mixture and stirred vigorously to determine the microemulsion region until the mixture became clear at a certain point. The concentrations of the components are recorded to construct pseudo-ternary phase diagrams, and then based on these results, the contents of oil, surfactant, co-surfactant and water at appropriate mass ratios are selected. After drawing a phase diagram based on the measurements, the obtained phase diagram allows to identify the regions of coarse emulsion and microemulsion.[21]

Formulation of microemulsion

After determining microemulsion region using pseudo-phase diagram, microemulsonis prepared by the spontaneous emulsification method. A certain amount of drug base is gradually dissolved in the oil phase, then the Smixis added and the final required amount of distilled water is added dropwise while gently stirring the mixture until a clear solution was obtained. The formulations are stored at room temperature and evaluated for clarity, drug precipitation and phase separation within 72h.

Characterization of prepared fluid microemulsion
Refractive Index (RI), pH, and Conductivity
The pH and electrical conductivity of microemulsionsare determined using a calibrated pH-meter and a conductivity meter respectively. The Refractive index of drug-loaded microemulsionsis measured by Refractometer.

Determination of Particle Size, polydispersity index and Zeta Potential
Mean droplet size, polydispersity index (PDI), and zeta potential of microemulsion formulations are measured at 25°C, using a Zetasizer.

Determination of Viscosity and Rheological Behaviour
A Brookfield cone and plate viscometer is used to measure the viscosity and examine the rheological behaviour of microemulsion formulations.

Drug content
Drug based microemulsion will be subjected to extract API from microemulsion in appropriate solvent. Suitable dilution is made with solvent and concentration will be measured by suitable analytical method such as HPLC, UV spectroscopy.

Stability study
The liquid microemulsion will be stored in a sealed glass vial at 25°C for 15 months and observed for macroscopic changes including turbidity, phase separation, drug precipitation and colour change.

Preparation of drug loaded microemulsion based gel
After characterization and stability study of microemulsion, the optimized formulation is applied for preparation of hydrogel. Microemulsions have low viscosity and are not suitable for topical applications. Gel base is prepared by dissolving suitable gelling agents like carbomer 934, carbomer 940 etc., in the distilled water. Then preparedmicroemulsionis added dropwise into gel base with continuous stirring to form microemulsion based gel.

Gel Characterization
Spread ability
To measure spread ability of microemulsion based gels, a circle with 1cm in diameter is marked on a glass plate. Half a gram of the test gel is placed on the circle, and a second glass plate was placed on the gel. A 5g weight is put on the upper glass plate, and after 5 min, the weight is removed, and the diameter of the spread gel is measured and reported.

pH Measurement
One gram of microemulsion based gels is mixed with 99g distilled water and stirred thoroughly until a uniform mixture is obtained. This solution will be used to measure the pH of microemulsion based gels.

Determination of Viscosity and Rheological Behaviour
Viscosity and rheological properties of the microemulsion based gels will be determined at 25±1°C, using a Brookfield viscometer.

Stability Tests
Stability of the selected microemulsion based gel will also be evaluated for 6 months at room temperature, 2-8°C and 40 ± 2°C (relative humidity: 75 ± 5%), and their appearance and viscosity will be examined.

Drug content
Drug loadedmicroemulsion based gels will be subjected to extract drug from microemulsion based gels in appropriate solvent. Suitable dilution ismade with solvent and concentration will be measured by suitable analytical method such as HPLC, UV spectroscopy.

In-vitrodrug release
In-vitro release tests will be performed using static Franz diffusion cells, this technique is an appropriate method to assess the drug release from topical formulations.[22]

Skin irritation test
Microemulsions contain a high amount of surfactants and/or co-surfactants, which may cause skin irritation when applied topically. Therefore, skin irritation studies have been conducted to assess the potential irritating effects. Skin irritation testing will be performed using animal studies. Usually, mice are used for this test. The formulation is applied to the skin of mice and any adverse allergic reactions that may occur are observed.

Researches carried out on microemulsion based gel
Drugs that are formulated as microemulsion based gels and researched for topical application:

Table 1: The accumulated research done on MBGs and their applications.

S.NO.	DRUG	Application	Conclusion	Reference
1	Tazarotene (TZR)	Therapy of acne	The gel has good tolerability, strong skin permeability, high cutaneous absorption, and suitable physicochemical characteristics.	[23]
2	Fusidic acid	Antibiotics	Strong stability, a high drug-loading capacity, strong antibacterial activity, and the potential to hasten wound healing are all displayed by the gel.	[24]
3	leflunomide/ diclofenac sodium	Rheumatoid arthritis.	MBGs showed sustained release, good stability and good bioavailability. It exhibited better anti-rheumatic activity results compared to conventional gels.	[25]
4	Celecoxib (CLX)	Arthritis	MEG was elastic and suitable for skin application, controlled release of CLX achieved, improved therapeutic effects for arthritis conditions	[26]
5	Cyclosporine	Psoriasis	According to the study, using customised microemulsion-gel could be a useful tactic to increase cyclosporine penetration and depot effect for psoriasis treatment.	[14]
6	Methotrexate (MTX)	Psoriasis	The MTX MEGs transdermal penetration increase 6 folds.	[27]
7	Clotrimazole	Antifungal	Indicating that in order to improve the effectiveness of cutaneous administration, the microstructure is a crucial formulation variable.	[28]
8	Repaglinide (RPG)	Hypoglycaemic activity	RPG microemulsion gel showed high in vitro drug permeation, andstatistically significanthypoglycaemic activity showed compared tooralRPG suspension in normal Sprague-Dawley rats.	[29]
9.	Isotretinoin (ITR) and erythromycin estolate (ES)	Acne	The in-vitro efficacy and ex-vivo skin permeation and drug deposition potential of a rheologically acceptable, scalable and transparent (aesthetic) product.	[30]
10	Indirubin (IR)	Anti-Psoriatic	The ME was physically stable, nano-sized, spherical, and with a narrow-size distribution, ME gel highly improved the permeation rate in vitro, suggested that IR-loaded ME formulation could be used for topical administration in the treatment of psoriasis or other topical skin disorders.	[31]

CONCLUSION

The limitations of gels can be overcome by microemulsionbased gels, which is accommodate hydrophobic drugs and improve the permeation of drug moieties in transdermal drug delivery systems. The development of microemulsion gels as a new drug delivery technology is still in its early stages. Microemulsion gels have shown excellent biocompatibility, sustained release, and improved drug permeability in studies.

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