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MICROEMULSION AS ADVANCED TOPICAL DRUG DELIVERY: A REVIEW

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ABSTRACT

Microemulsions (MEs) are clear, thermodynamically stable systems. They were used to solubilize drugs and to improve topical drug availability. The formulation of microemulsion for pharmaceutical use requires a thorough understanding of the properties, uses, and limitations of microemulsion. Three distinct microemulsions – oil external, water external and middle phase can be used for drug delivery, depending upon the type of drug delivery upon the type of drug and the site of action. While microemulsions are used in several fields, this article we focuses on the recent development of microemulsion.

KEYWORD: Microemulsion, Topical delivery, Applications.

INTRODUCTION

Topical preparations pertain to medicaments applied to the surface of a part of the body and is a term used to describe formulations that have effects only in a specific area of the body and are formulated in such a manner that the systemic absorption of the medicament is minimal. The methods involved in conventional topical drug delivery basically involve either assisting or manipulating the barrier function of the skin (topical antibiotics, antibacterial, emollients, sunscreen agents) the horny layer at the molecular scale so as to direct drugs to the viable epidermal and dermal tissues without using oral, systemic or other therapies.[1]

Topical drug delivery can be defined as application of drug via skin to directly treat or cure the skin disorders. These systems are generally used for local skin infection like fungal infection or in place where other routes of the drug administration fails. These preparations are applied onto the skin surface for providing local or systemic effects. Topical route favors safe and effective delivery of drug molecules with lower doses as compared to the conventional system.[2]

Microemulsions are thermodynamically stable isotropic systems in which two immiscible liquids (water and oil) are mixed to form a single phase by means of an appropriate surfactant or its mixture. The short to medium chain alcohols are generally considered as co-surfactants in the microemulsion system. The presence of surfactant and cosurfactant in the system makes the interfacial tension very low. Therefore, microemulsions form spontaneously, with an average droplet diameter of 10 to 140 nm.[3]

Microemulsions have the ability to deliver larger amounts of water and topically applied agents into the skin than water alone or other traditional vehicles such as lotions or creams because they act as a better reservoir for a poorly soluble drug through their capacity for enhanced solubilization.[4]

Components of Microemulsions

A large number of oils and surfactants are available which can be used as components of microemulsion systems but their toxicity, irritation potential and unclear mechanism of action limit their use. One must choose materials that are biocompatible, non-toxic, clinically acceptable, and use emulsifiers in an appropriate concentration range that will result in mild and nonaggressive microemulsions.

- **Oil:** Ethyl oleate, Mineral oil, Isopropyl myristate, Decanol, Oleic acid, Vegetable oils (Coconut oil, Safflower oil, Soyabean oil, Olive oil), Medium chain length triglyceride (Mygliol 812).
- **Surfactant:** Polysorbate (Tween 80 and Tween 20), Lauromacrogol 300, Lecithins, Decyl polyglucoside (Labrafil M 1944 LS), Polyglyceryl-6-dioleate (Plurol Oleique), Dioctyl sodium sulfosuccinate (Aerosol OT), PEG- 8 caprylic/capril glyceride (Labrasol).
- **Co-surfactant:** Sorbitan monooleate, Sorbitan monostearate, Propylene glycol, Propylene glycol monocaprylate (Capryol 90), 2-(2-ethoxyethoxy)ethanol (Transcutol P) and Ethanol.[5]

Types of Microemulsions

Microemulsions are thermodynamically stable, but are only found under carefully defined conditions. According to Winsor, there are four types of microemulsion phases exists in equilibria, these phases are also referred as Winsor phases. They are,

1. Oil- in- water microemulsion or winsor I
2. Water – in oil microemulsion or winsor II
3. Bicontinuous microemulsion or winsor III
4. Single phase homogeneous mixture or winsor IV

1. Oil- in- water microemulsion or winsor I

In Oil-in-water type of microemulsions droplets of oil is surrounded by a surfactant (and may be cosurfactant) film that forms the internal phase distributed in water, which is the continuous phase. This type of microemulsion generally has a larger interaction volume than the w/o microemulsions.

2. Water - in - oil microemulsion or winsor II

In Water-in-oil type of microemulsions droplets of water surrounded by a continuous oil phase. These are recognized as "reverse micelles", where the polar head groups of the surfactant are facing into the droplets of water, with the fatty acid tails facing into the oil phase. A w/o microemulsion used orally or parenterally may be destabilized by the aqueous biological system.

3. Bicontinuous microemulsion or winsor III

In bicontinuous microemulsion system the amount of water and oil present are similar, In this case, both water and oil exist as a continuous phase. An irregular channel of oil and water are combined, and looks like a "sponge-phase". Transitions from o/w to w/o microemulsions may pass through this bicontinuous state. Bicontinuous microemulsion, may show non-Newtonian flow and plasticity. These properties make them especially useful for topical delivery of drugs or for intravenous administration.

4. Single phase homogeneous mixture or winsor IV

In single phase homogeneous mixture or winsor IV the oil, water and surfactants are homogenously mixed.[6]

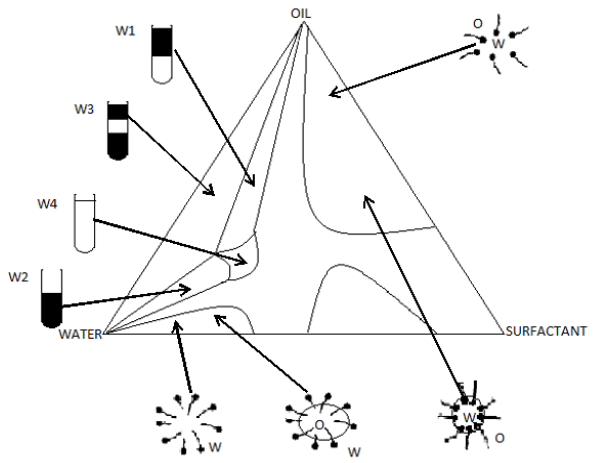

Fig. 1: Types of Microemulsion system.

Advantages of Microemulsion

Microemulsions system has considerable potential to act as a drug delivery vehicle by incorporating a wide range of drug molecules.

1. Good thermodynamically stable and inexpensive.
2. It is used in the wide range of pharmaceuticals and cosmetics formulation.
3. It is used as a vehicle for topical, oral, nasal and transdermal applications.
4. It is used as bioavailability enhancers for poorly water soluble drug.
5. It acts as a penetration enhancer and 'super solvents' of drug.
6. Long shelf life.
7. Wide applications in colloidal drug delivery systems for the purpose of drug targeting and controlled release
8. Helpful in taste masking.[7]

Disadvantages Of Microemulsion

1. Use of a large concentration of surfactant and co-surfactant necessary for stabilizing nano droplets.
2. Limited solubilizing capacity for high melting substances.
3. The surfactant must be nontoxic for using pharmaceutical applications.
4. Microemulsion stability is influenced by environmental parameters such as temperature and pH. These parameters change upon microemulsion delivery to patients.[8]

Applications of Topical Microemulsion

Microemulsions are promising delivery systems that allow sustained or controlled drug release for percutaneous, peroral, topical, and transdermal, administration. Enhanced absorption of drugs, modulation of the kinetics of the drug release and decreased toxicity are several advantages in the delivery process.

The following is a application of topical microemulsions.-

Antifungal

Superficial mycoses usually respond to topical therapy. In the Settling of eczema, topical antifungal agents such as ketoconazole are used to reduce the fungal infection caused by Pityrosporum ovale or Malassezia furfur. Antifungal agents e.g miconazole, ketoconazole, and itraconazole being lipophilic in nature have been formulated as microemulsions to impart to them the advantages like ease of preparation due to spontaneous formation, thermodynamic stability, transparent and elegant appearance, increased drug loading, enhanced penetration through the biological membranes, increased bioavailability compared between conventional dosage forms.

Antiviral
A study was done to investigate and evaluate microemulsion and microemulsion-based hydrogel as a topical delivery system for penciclovir in comparison with a commercial cream.

Acyclovir containing microemulsion-based formulations for topical delivery were developed using isopropyl myristate/Captex 355/Labrafac as an oil phase, Tween 20 as surfactant, Span 20 as cosurfactant, and water dimethyl sulfoxide as an aqueous phase.

Anti acne
Novel drug delivery strategies like microemulsions can play a pivotal role in improving the topical delivery of antiacne agents by enhancing their dermal localization with a concomitant reduction in their side effects. Micro emulsions of azelaic acid, a bioactive molecule used in many skin disorders, prepared using the monosodium salt have been evaluated as delivery vehicles.

Microemulsions in Cosmetic preparation
In many cosmetic applications such as skin care products, emulsions are widely used with water as the continuous phase. It is believed that microemulsions formulation will result in a faster uptake into the skin. Cost, safety (as many surfactants are irritating to the skin when used in high concentrations), appropriate selection of ingredients (i.e. surfactants, co-surfactants, oils) are key factors in the formulation of microemulsions.[9]

Recent Trends & Future Developments
During the last two decades lot of research work has been carried out on microemulsion system for providing novel solutions to overcome the problems of poor aqueous solubility of highly lipophilic drug compounds and provide reproducible bioavailability. Industrial point of view, it can be easily scaled up with considering relative cost of commercial production. Microemulsion can also be used for cosmetic purpose and drug targeting. Now a day, researcher work is focused on the production of safe, efficient and more compatible microemulsion constituents which will further enhance the utility of this novel delivery system. One hopes that our society will be able to muster the collective financial and moral courage to allow such extraordinarily powerful drug delivery carrier to be deployed for human betterment, with due regard to essential ethical considerations.[10]

Table No. 1: Recently Reported Topical Delivery System of Microemulsions.

Sl No	Drug	Oil	Surfactant/ Co-surfactant	Method of preparations	Report
01	Acyclovir[11]	Labrafil M, Capryol 90	Tween-80, n-butanol	Ultrasonication	Ramdan *et al* (2013)., The release pattern of the drug was affected by the water content in the system. The percent drug release increased by increasing the water content of microemulsion.
02	Levofloxacin[12]	Oleic acid	Tween60, Isopropyl alcohol	Phase titration method	Prajapathi *et al*(2013)., Levofloxacin microemulsion system may be the most convenient topical formulation for the patient unable to take drug orally.
03	Sertaconazole nitrate[13]	Eugenol, Oleic acid	Tween-80, Transcutol-P, propylene glycol	Ultrasonication.	Muzaffar *et al*(2017)., Have great potential for topical drug delivery in the treatment of inflammation and fungal infection.
04	Salicylic acid[14]	Neem oil	Labrasol, Plurol oleique	Magnetic stirring	Bharade *et al*(2019)., The solubility and permeability of Salicylic acid can be increased by formulating into micro emulsion gel. Salicylic acid was able to increase the efficacy of the currently available commercial products for the topical treatment of psoriasis.
05	Griseofulvin[15]	Oleic acid	Tween 80, Ethanol	Vortexing	Aggarwal *et al* (2013)., Microemulsion formulation of griseofulvin for the treatment of dermatophytosis. Provide better remission from the disease due to localized delivery with minimal side effects.
06	Miconazole Nitrate[16]	Oleic acid, olive oil,	Tween-20, propylene glycol	Magnetic stirring	Shahzadi *et al*(2014)., Miconazole nitrate can be formulated as micro emulsion with good release and

					consistency.
07	Dexamethasone[17]	Labrafac, Transcutol P	Tween 80, Labrasol, capryol 90	Magnetic stirring	Salimi *et al* (2013)., Microemulsions make good solubility of dexamethasone with vast range of microstructures. Performed to elucidate the mechanisms of drug delivery into the skin.
08	Terbinafine Hcl[18]	Propylene glycol	Tween-80, Poluethylene glycol-400	Vortexing	Shrestha *et al* (2017)., Develop a novel drug delivery system with enhanced therapeutic efficacy by improving the solubility, permeability and increased the bioavailability of a poorly water soluble drug.
09	Salicylic acid, Clobetasol propionate[19]	Oleic acid	Labrasol, Trasctol-P	Water titration method	Trivedi *et al*(2018)., exhibit better skin retention in comparison with conventional formulation and in-vivo anti psoriasis activity studies prove that the developed microemulgel formulation can be a promising product in the treatment of Psoriasis.
10	Valacyclovir Hcl[20]	Iso propyl myristate, Oleic acid,	Tween-80, Span-80, Ethanol, Di Methyl Sulfoxide	Magnetic stirring	Kamaria *et al* (2015)., Hydrogel based Microemulsion of valacyclovir Hydrochloride provide a basis for successful design of topical delivery.

Table No. 2: Microemulsions based marked products.

Brand Name	Composition	Manufactured by
Sandimmune Neoral®	Cyclosporin	Novartis
Fortovase®	Saquinavir	Roche Laboratories
Norvir®	Ritonavir	Abbott Laboratorories

REVIEW OF LITRETURE

Badawi *et al* (2009)., have prepared microemulsion system containing salicylic acid. They used Isopropyl myristate as oil phase and Tween 80, Propylene glycol as surfactant and co-surfactant to develop microemulsion. Further in their study they incorporate different concentration of Salicylic acid into microemulsion gel base remarkably decreases the viscosity of the base without affecting its isotropic nature and concentration of salicylic acid increases, the percent transmittance and the specific gravity of the system also increases. Finally they reported that microemulsion could be a suitable vehicle for topical application.[21]

Maher *et al* (2017)., studied the microemulsion preparation composed of 12% Salicylic acid and 4% of Lactic acid using castor oil, tween 80, propylene glycol, ethyl alcohol and purified water. They constructed four pseudo ternary phase diagrams by using the low energy emulsification technique and studied for 75 days under a titration method using purified water (with or without propylene glycol), each phase diagram was investigated at 25°C, 37°C and 45°C. Their results clearly indicated that the resulted microemulsion liquid were clear and thermodynamic at all temperatures of study, and using propylene glycol as a co-surfactant, lead to more stable microemulsions by using low concentration of tween 80.[22]

Panapisal *et al* (2012)., studied the potential of several microemulsion formulations for dermal delivery of Silymarin was evaluated. They construct pseudo ternary phase diagrams for the various microemulsion formulations using Glyceryl monooleate, Oleic acid, Ethyl oleate or Isopropyl myristate as the oil phase, a mixture of Tween 20, Labrasol or Span 20 with HCO-40 (1:1 ratio) as surfactants and Transcutol as a co-surfactant. Oil-in-water microemulsions were selected to incorporate 2% W/W Silymarin. The Silybin remainings depends on the type of surfactants and were sequenced in the order of Labrasol > Tween 20 > span 20. They studied in vitro release shows. prolonged release to microemulsions when compared to Silymarin solubility. Finally they reported that microemulsions containing Labrasol were suitable to enhance Silymarin solubility.[23]

Salimi *et al* (2012)., formulate transparent microemulsion based topical delivery system containing Tretinoin. They used Isopropyl myristate-Transcutol P (10:1 ratio) as the oil phase, Tween 80 and Labrasol as the surfactant and Propylene glycol as the co-surfactant to develop microemulsion. They showed that the maximum oil was incorporated to microemulsion system it contains surfactants and cosurfactants ratio (Km) of 4:1. They revealed that centrifugation test of microemulsions were remained homogenous without any phase separation and the test showed good physical stability of preparations. They have droplet size of

microemulsion in the range of 14.1 to 36.5nm and viscosity ranges was found to be 200 to 350 Cps. The reported that the drug release profile showed 49% in the first 8 hours. Finally they concluded that microemulsion were preferable for topical formulation.[24]

Jantrawut *et al* (2018)., developed orange oil microemulsion and investigated the antimicrobial activity of film containing orange oil microemulsion. They developed pseudo-ternary phase diagrams and study the influences of surfactant and co-surfactant mass to optimized microemulsion-loaded-films. They reported the microemulsion formulations with particle size range of about 60.26–80.00 nm, with broad polydispersity index of 0.42. Their study revealed that orange oil microemulsion films exhibited higher elastic values and finally concluded that the antibacterial activity of orange oil in pectin thin film could be enhanced by preparing orange oil as an microemulsion before loading into pectin thin film.[25]

CONCLUSION

Microemulsions are commercially feasible, simple and convenient novel vehicles for delivery of medicaments which can enhance drug absorption with reduced systemic side effects. They can be used to optimise drug targeting without a concomitant increase in systemic absorption. Appropriate excipient selection and safety evaluation especially of the co-surfactants is crucial in the formulation of microemulsions. They can be potential drug delivery systems for the delivery of more than one medicament simultaneously.

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