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Review Article

An Overview on Microemulsion as a Topical Drug Delivry System

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A B S T R A C T

Due to their extended shelf life, enhanced drug solubilization, and simplicity in preparation and administration, microemulsions are among the greatest possibilities for new drug delivery systems. Microemulsions are liquid mixtures of amphiphile, water, and oil that are thermodynamically stable and optically isotropic. They have become cutting-edge drug delivery systems that enable controlled or sustained release for parenteral, ophthalmic, percutaneous, topical, and transdermal medication administration.Because of their low viscosity, transparency, and, more precisely, their thermodynamic stability, microemulsions may be easily distinguished from regular emulsions. Microemulsions have a wide range of uses and applications, including in the pharmaceutical, agrochemical, cutting oil, biotechnology, food, and cosmetic industries as well as in analytical applications and environmental detoxification. This review paper's main goal is to talk about using microemulsions as a medicine delivery mechanism with other potential uses.

Key words: TDDS, Microemulsions, thermodynamically stable, amphiphile, solubilization

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INTRODUCTION

Transdermal Drug Delivery Systems [1, 2]

One of the most promising drug application techniques at the moment is transdermal drug delivery. The list of therapeutic compounds that can be administered to the systemic circulation via skin is being expanded to include an increasing number of medications.Transdermal drug delivery systems (TDDS) are self-contained discrete dose forms that release the medication(s) to the systemic circulation at a controlled pace through the skin when applied to intact skin. Since several years ago, it has been possible to administer drugs via unbroken skin. The idea of delivering drugs through the skin dates back to prehistoric times. Castor oil plant bark was ingested with water and applied to an aching head by Ebers Papyrus. The medicated plaster, which became highly well-liked in Japan as an over-the-counter medicinal dosage form, can be seen historically as the first creation of transdermal drug delivery.

Transdermal delivery not only offers controlled, ongoing medication administration but also enables continuous administration of medications with brief biological half-lives and prevents pulsed entrance into the systemic circulation, a frequent unwanted side effect. For systemic effects, TDDS make it easier for therapeutic doses of pharmacological compounds to pass through the skin and into the bloodstream.

Transdermal delivery not only permits continuous, controlled medicine administration but also allows for the continuous administration of drugs with short biological half-lives and avoids pulsed admission into the systemic circulation, a common unintended side effect. TDDS facilitate the faster transdermal absorption of therapeutic dosages of pharmacological substances for systemic effects.

Transdermal delivery not only permits continuous, controlled medicine administration but also allows for the continuous administration of drugs with short biological half-lives and avoids pulsed admission into the systemic circulation, a common unintended side effect. TDDS facilitate the faster transdermal absorption of therapeutic dosages of pharmacological substances for systemic effects. In terms of cutaneous application, microemulsions may interact

with the stratum corneum to alter the lipid layer's structural organisation, improving transdermal drug permeability and serving as a penetration enhancer.

Advantages of TDDS [3]

- Avoidance of first pass metabolism
- Avoidance of gastro intestinal incompatibility
- Predictable and extended duration of activity
- Minimizing undesirable side effects
- Provides utilization of drugs with short biological half life
- Narrow therapeutic window
- Improving physiological and pharmacological response
- Avoidance the fluctuation in drug levels
- Termination of therapy is easy at any point of time
- Greater patient compliance due to elimination of multiple dosing profile
- Ability to deliver drug more selectively to a specific site
- Provide suitability for self administration
- Enhance therapeutic efficacy.

Limitations of TDDS

- Transdermal route administration is unsuitable for drugs that irritate or sensitize the skin.
- Transdermal route cannot deliver in a pulsatile fashion.
- Transdermal delivery is neither practical nor affordable when required to deliver large doses of drugs through skin.
- Transdermal delivery cannot administer drugs that require high blood levels .
- Drug of drug formulation may cause irritation or sensitization.
- Not practical, when the drug is extensively metabolized in the skin and when molecular size is great enough to prevent the molecules from diffusing through the skin.
- Not suitable for a drug, which doesn't possess a favourable, O/W partition coefficient.
- The barrier functions of the skin of changes from one site to another on the same person, from person to person and with age.

THE HUMAN SKIN [4]

Transdermal is a very effective alternate delivery technique. A typical adult's skin has a surface area of around 2 metres, and it gets about one-third of the blood that circulates through the body. It is required to comprehend the skin in order to transport a medicine into the body through the transdermal layer of skin.

The skin serves as the body's outermost layer. It protects the underlying muscles, bones, ligaments, and internal organs in humans and is the largest organ of the integumentary system. It is made up of numerous layers of epithelial tissues. The average adult's skin is between 1.5 and 2 m2 (16.1-21.5 sq ft) in surface area and is mostly between 2.3mm (0.10 inch) thick. The average square inch (6.5cm2) of skin has more than a thousand nerve endings, 650 sweat glands, 20 blood arteries, and 60,000 melanocytes. It carries out a number of crucial duties. Literally translated from Latin, the adjective cutaneous means "of the skin" (cutis, skin).Figure 1 depicts the several layers of the human skin.

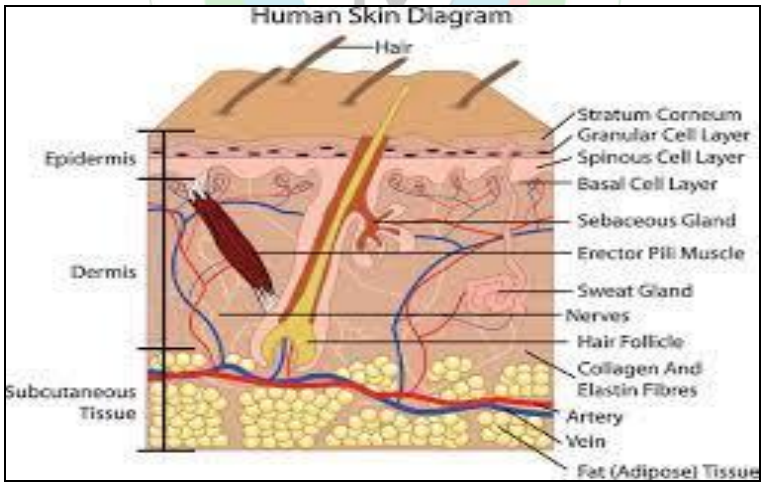

Figure.1: Structure of human skin

Anatomy of the Skin

The skin is composed of two main structural components. The epidermis is the outer, thinner layer that is made up of epithelium. The inner, denser, connective tissue layer known as the dermis is joined to the epidermis. There is a subcutaneous layer underneath the dermis. The superficial fascia or hypodermis are other names for this layer. Areoles and adipose tissues make up this tissue. The skin is fixed to the subcutaneous layer by fibres from the dermis that descend there. In turn, the subcutaneous layer adheres to the underlying organs and tissues.

Skin layers:

Skin is composed of three primary layers.

- Epidermis
- Dermis
- Hypodermis (subcutaneous adipose layer).

MICROEMULSION [5,6]

Hour and Schulman first used electron microscopy to identify tiny emulsion-like formations in 1943, and they later came up with the word "microemulsions". While the diameter of droplets in a kinetically stable emulsion is

>500 nm, microemulsions are isotropic, thermodynamically stable transparent (or translucent) systems of oil, water, and surfactant, frequently in combination with a co-surfactant. A microemulsion has benefits as a carrier for medications that are poorly soluble in water because of the microscopic droplets. These homogeneous systems are all low viscosity fluids that can be created with a variety of surfactant concentrations and oil to water ratios.

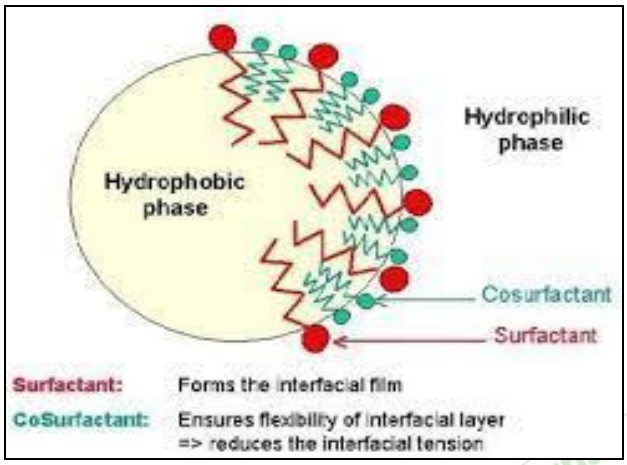

Figure.2: Structure of micro emulsion

Important Characteristics of Microemulsions [7,8]

- Particle size 10-100 nm
- Thermodynamically stable (long shelf-life)
- Optically clear
- High surface area (high solubilization capacity)
- Small droplet size
- Enhanced drug solubilization
- Ease formation (zero interfacial tension and almost spontaneous formation)
- Ability to be sterilized by filtration
- Long-term stability
- High solubilization capacity for hydrophilic and lipophilic drugs
- Improved drug delivery.

Advantages of Microemulsion [9]

- Thermodynamically stable and require minimum energy for formation
- To increase the cutaneous absorption of both lipophilic and hydrophilic drugs when compared to conventional vehicles (emulsions, pure oils, aqueous solutions).
- Ease of preparation and high diffusion and absorption rates when compared to solvent without the surfactant system
- The formation of microemulsion is reversible. They may become unstable at low or high temperature but when the temperature to the stability range, the microemulsion reforms
- Drugs that are thermo-labile are easily incorporated without the risk of degradation
- Microemulsions act as supersolvent of drug. They can solubilize hydrophilic and lipophilic drugs including drugs that are relatively insoluble in both aqueous and hydrophobic solvents.
- This system is reckoned advantages because of its wide applications in colloidal drug delivery systems for the purpose of drug targeting and controlled release.
- A large amount of drug can be incorporated in the formulation due to the high solubilizing capacity that might increase thermodynamic activity towards the skin
- The surfactant and co surfactant in the microemulsions may reduce the diffusional barrier of the stratum corneum by acting as penetration enhancers.
- Low surface tension ensures good contact to the skin. Also, the dispersed phase can act as a reservoir making it possible to maintain an almost constant concentration gradient over the skin for a long time.

Disadvantages of Microemulsion

- Use of large concentration of surfactant and co-surfactant necessary for stabilizing the nanodroplets.
- Limited solubilizing capacity for high-melting substances
- The surfactant must be nontoxic for using pharmaceutical applications
- Microemulsion stability is influenced environmental parameters such as temperature and pH. These parameters change upon microemulsion delivery to patients.

STRUCTURE OF MICROEMULSION[10]

Depending on the component ratios, the mixture of oil, water, and surfactants can generate a wide range of structures and phases. In this context, the surfactant film's flexibility is crucial. The spectrum of structures that can exist in a microemulsion will be expanded by a flexible surfactant layer, including aggregates, bicontinuous structures, droplet-like shapes, and more. Bicontinuous structures cannot exist in an extremely stiff surfactant coating, which limits the range of existence.In addition to microemulsions, structural analyses can show the presence of normal emulsions, anisotropic crystalline hexagonal or cubic phases, and lamellar structures depending on the component ratio. The diffusivity of the phases, and consequently the dispersion of a medication in each phase, are both significantly influenced by the internal structure of a microemulsion vehicle. To comprehend the complex phase behaviour and thenumerous microstructures seen in the microemulsion systems, researchers have been working arduously.

Components of Microemulsion Formulations [11]

There are many oils and surfactants that can be utilised as microemulsion system components, but their use is restricted due to their toxicity, potential for irritability, and unknown mode of action. In order to produce mild and non-aggressive microemulsions, one must select materials that are biocompatible, non-toxic, and clinically acceptable. Emulsifiers must also be used in the proper concentration range. Therefore, the use of generally recognised as safe (GRAS) excipients is stressed.

Oil Phase:

The capacity of the oil component to permeate and subsequently swell the tail group region of the surfactant monolayer affects curvature. In comparison to long chain alkanes, short chain oils more deeply penetrate the tail group region, causing this region to expand and produce an increase in negative curvature (and a decrease in effective HLB). Both saturated (such as lauric, myristic, and capric acid) and unsaturated (such as oleic, linoleic, and linolenic acid) fatty acids have long been researched for their ability to increase penetration.. As the oil phase, fatty acid esters like the ethyl and methyl esters of lauric, myristic, and oleic acids have also been used. O/W microemulsions are preferred for solubilizing lipophilic medicines. The drug's great solubility in the oil phase is the primary factor for choosing it. In order to give the therapeutic dose of the medicine in an encapsulated form, this will reduce the volume of the formulation.

Surfactants:

The chosen surfactant must be able to provide a flexible film that can easily deform around the droplets and be of the appropriate lipophilic character to provide the correct curvature at the interfacial region. This will facilitate the dispersion process during the preparation of the microemulsion.

It is well acknowledged that low HLB surfactants are preferable for creating w/o microemulsions while high HLB surfactants (>12) are preferred for creating o/w microemulsions. The addition of co-surfactants is frequently necessary for surfactants with HLB larger than 20 to reduce their effective HLB to a value within the range needed for microemulsion production.

Co-surfactants:

Most of the time, single-chain surfactants are unable to adequately lower the o/w interfacial tension to allow a microemulsion to develop on their own. Co-surfactants give the interfacial film the flexibility it needs to adopt the many curvatures necessary to create microemulsions over a wide range of composition. The lipophilic chains of the surfactant should be suitably short or contain fluidizing groups (such as unsaturated bonds) if a single surfactant film is desired. As co-surfactants, short to medium chain length alcohols (C3-C8) are frequently used to increase the fluidity of the contact and further lower interfacial tension.

METHOD OF PREPARATION OF MICROEMULSION[12]:

Phase Titration Method

Phase diagrams can be used to represent microemulsions, which are created using the spontaneous emulsification technique (also known as the phase titration technique). The creation of phase diagrams is a helpful method for studying the intricate web of interactions that might develop when several components are combined. Depending on the chemical makeup and concentration of each component, microemulsions are created along with a variety of association structures (including emulsion, micelles, lamellar, hexagonal, cubic, and different gels and oily dispersion). The study's key components include understanding their phase equilibria and defining the phase boundaries.

In order to locate the various zones, including the microemulsion zone, where each corner of the figure represents 100% of the specific component, pseudo ternary phase diagrams, which are quicker to produce and easier to understand, are frequently used instead of quaternary phase diagrams (four component systems).By only taking into account the compositionwhether it is oil- or water-rich—the area can be divided into w/o or o/w microemulsion. It is important to make cautious observations to avoid observing the metastable systems.

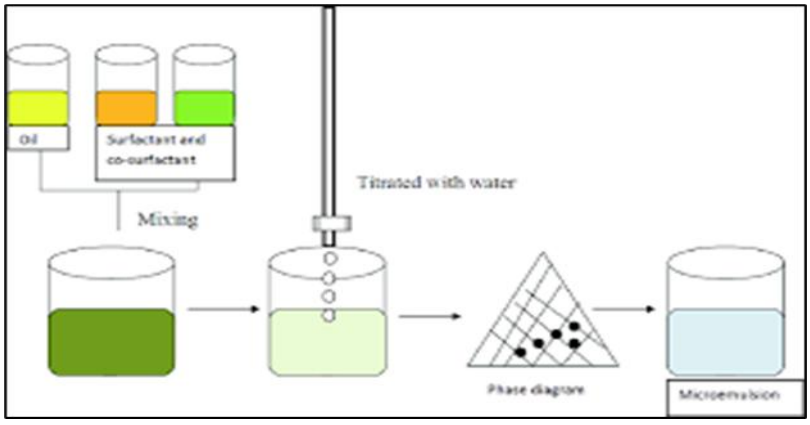

Figure.3: Phase titration method

Phase Inversion Method

Microemulsions experience phase inversion when too much of the dispersed phase is added or when the temperature changes. Significant physical changes, such as changes in particle size, occur during phase inversion and may have an impact on drug release both in vivo and in vitro. The phase inversion temperature (PIT) method is the name of this technique. Other factors, such as salt concentration or pH value, may be taken into account in addition to or instead of temperature. Changing the water volume fraction can also result in a change in the spontaneous radius of curvature. Water droplets are originally created in a continuous oil phase by adding water to it in small amounts at first. When the water volume percentage is increased, the surfactant's spontaneous curvature shifts from initially stabilising aw/o microemulsion to an o/w microemulsion at the inversion locus.

In order to create clear solutions with dispersions of either water-in-oil (w/o) or oil-in-water (o/w) in nanoscale or colloidal dispersions (100 nm), milky emulsions can be converted into microemulsions by carefully adding lesser alcohols (butanol, pentanol, and hexanol) to milky emulsions. The lower alcohols are known as co-surfactants, because they reduce the interfacial tension between oil and water to a level where formation is nearly spontaneous. The overall composition, which is system-specific, determines the miscibility of oil, water, and amphiphile (surfactant plus co-surfactant).

In the industrial world, microemulsions are used for a variety of processes, including the manufacture of polymers. Transport of monomers, free radicals, and other species (such as chain transfer agents, co-surfactants, and inhibitors) between the aqueous and organic phases occurs during the complicated heterogeneous process known as microemulsion polymerization. Microemulsion polymerization is a more complex system when compared to other heterogeneous polymerization techniques (suspension or emulsion). The partitioning of monomers among the phases, particle nucleation, and radical adsorption and desorption all affect the rate of polymerization. The quantity, kind, and pH of the dispersion medium all affect particle stability.

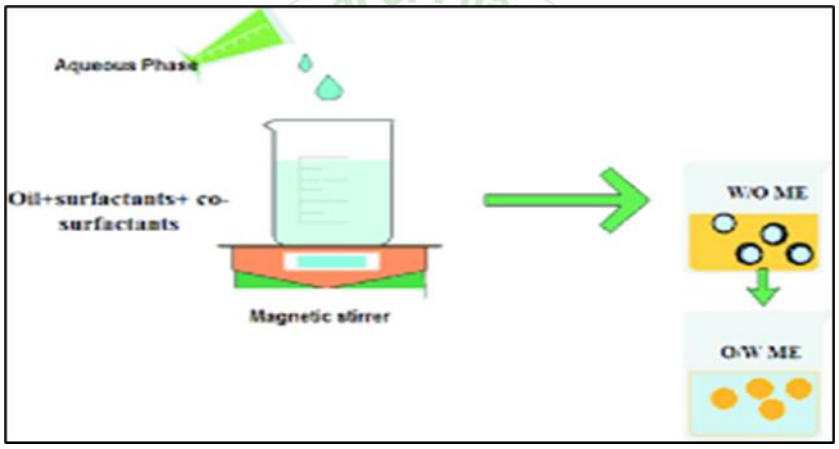

Figure.4: Phase inversion method

Types of microemulsion [13-15]

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. Bicontinuousmicroemulsion or winsor III
4. Single phase homogeneous mixture or winsor IV

1. Oil- in- water microemulsion or winsor I

A surfactant (and sometimes a cosurfactant) coating surrounds the oil droplets in an oil-in-water type microemulsion, forming the internal phase that is dispersed in water and is the continuous phase. In comparison to microemulsions without, this kind often has a greater interaction volume.

2. Water - in - oil microemulsion or winsor II

A continuous oil phase surrounds water droplets in a water-in-oil type microemulsion. These are referred to as "reversemicelles" because the polar headgroups of the surfactant are directed towards the water droplets, while the fatty acid tails are directed towards the oil phase. When administered parenterally or orally, a w/o microemulsion may become unstable due to the aqueous biological system.

3. Bicontinuousmicroemulsion or winsor III

The amount of water and oil present in a bicontinuous microemulsion system is comparable. In this situation, both water and oil exist as a continuous phase. A "sponge-phase" is createdwhen an uneven channel of water and oil is combined. It is possible for o/w to w/o microemulsion transitions to go through this bicontinuous stage. Bicontinuousmicroemulsions may exhibit plasticity and flow that are not Newtonian. These qualities

make them especially beneficial for intravenous administration or topical medication delivery.

4. **Single phase homogeneous mixture or winsor IV**

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

FACTOR AFFECTING FORMULATION OF MICROEMULSION SYSTEM (16-18)

Property of surfactant

There are two categories of lipophilic and hydrophilic groups in surfactant. Hydrophilic single chain surfactants have a tendency to generate o/w microemulsions and totally dissociate in diluted solutions. The degree of polar group dissociation decreases when the surfactant is present in salt or when a high surfactant concentration is applied, and the resulting system may be typeless.

Property of Oil Phase

The capacity of the oil phase to penetrate and inflame the surfactant monolayer's tail group region, which results in enhanced negative curvature in the absence of microemulsion, also affects curvature.

Packing Ratio [19]

The type of microemulsion is determined by the surfactant's HLB through its impact on packing and film curvature. Analysis of film curvature for surfactant associations that result in microemulsion production.

Temperature [20]

The effective head group size of nonionic surfactants is strongly influenced by temperature. They form a typical o/w system at low temperatures because they are hydrophilic. They become lipophilic and lack systems at higher temperatures. A bicontinuous structure is created when a microemulsion coexists with excessive water and oil phases at a medium temperature.

EVALUATION PARAMETERS OF MICROEMULSION SYSTEM

Physical appearance

For Physical appearance microemulsion can be inspect visually for homogeneity, fluidity and optical clarity.

Scattering Techniques [21]

Studies of the structure of microemulsions have used scattering techniques like small angle neutron scattering, small angle X-ray scattering, and light scattering, particularly in the case of dilute monodispersed spheres in polydisperse or concentrated systems like those frequently found in microemulsions.

Limpidity Test (Percent Transmittance) [22]

A spectrophotometer can be used to spectrophotometrically determine the microemulsion's limpidity.

Drug stability [23]

The ideal microemulsion was stored at low temperature (4–8 °C), room temperature, and high temperature (50–2 °C). The microemulsion can be examined for phase separation, percent transmittance, globule size, and assay every two months.

Globule size and zeta potential measurements [24]

The globule size and zeta potential of the microemulsion can be determined by dynamic light scattering, using a Zetasizer HSA 3000.

Assessment of the Rheological Properties (viscosity measurement) [25]

The stability is significantly influenced by the rheological characteristics. The Brookfield digital viscometer can ascertain it. Rheological properties that change can be used to distinguish the microemulsion zone from other regions. Continual changes between the bicontinuous structure, swollen reverse micelle, and swollen micelles occur in bicontinuous microemulsions, which are dynamic structures.

Electrical conductivity [26]

A mixture of oil, surfactant, and co-surfactant was given a dropwise addition of the water phase. The electrical conductivity of the created samples was then evaluated using a conductometer at room temperature and at a constant frequency of 1 Hz.

Drug solubility [27]

The optimised microemulsion formulation and every component within received an excessive addition of drug. After 24 hours of nonstop stirring at room temperature, samples were taken out and centrifuged for 10 minutes at 6000 rpm. By deducting the drug contained in the sediment from the total amount of drug added, the amount of soluble drug in the optimised formulation as well as each individual ingredient of the formulation were estimated. Regarding each of the microemulsion's constituent ingredients, the drug's solubility was compared.

In-vitro drug release [28-29]

In a 20mL volume, a modified Franz diffusion cell can be used to conduct the diffusion investigation. With buffer, the receptor compartment was filled.The microemulsion formulation and the pure drug solution were contained separately in the donor compartment, which was fixed with a cellophane membrane. Samples were taken out of the receptor compartment at predefined intervals and put through a UV spectrophotometer at a particular wavelength to be analysed for drug content.

APPLICATION OF MICROEMULSION SYSTEM

Microemulsion in Pharmaceutical

From last two decades there has been a revolution in the utilization of microemulsion systems in a variety of pharmaceuticals.

Parenteral Delivery [30]

Due to the extremely poor drug delivery to a specific site, parenteral administration (particularly via the intravenous route) of medicines with restricted solubility is a significant issue in industry. When administered parenterally, microemulsion formulations have significant advantages over macroemulsion systems because the tiny particle microemulsion clears more slowly than the coarse particle emulsion and stays in the body for longer.

Oral Delivery [31]

The advantages of microemulsion formulations over traditional oral formulations include better clinical potency, reduced medication toxicity, and enhanced absorption. As a result, it has been claimed that microemulsions are the best delivery system for medications like steroids, hormones, diuretics, and antibiotics.

Topical delivery [32]

The avoidance of hepatic first-pass metabolism, salivary and stomach drug degradation, and related toxicity consequences are just a few of the benefits of topical medication administration over other approaches. Another is the drug's capacity to distribute itself directly to the skin or eyes that are damaged and to be targeted there. Numerous research on the topic of medication absorption through the skin have been conducted recently. They can integrate both lipophilic (5-fluorouracil, apomorphine hydrochloride, etc.) and hydrophilic (5-fluorouracil) medicines to increase their penetration. Since creating microemulsions needs a high surfactant concentration, skin irritation must be taken into account, especially if they are going to be administered for an extended period of time.

Ocular and Pulmonary Delivery [33-35]

Drugs are mostly used topically for the treatment of eye disorders. O/W microemulsions have been researched for ocular delivery, for the dissolution of poorly soluble medicines, for increasing absorption, and for achieving prolong release profiles.

REFERENCES

1. Chien YW. Transdermal Drug Delivery and Delivery Systems, in: Y.W.Chien, Novel Drug Delivery Systems, 2nd ed, Chapter 7, Marcel Dekker, New York, 1992: 301-380.
2. Vyas SP and Khar RK. Targetted and Controlled Drug Delivery Novel Carrier System 1st ed., CBS Publishers and Distributors, New Delhi, 2002:411-447.
3. Hadgraft J, Guy R. In; Transdermal Drug Delivery, Marcel Dekker, Inc., New York and Basel,35,296.
4. Prausnitz MR, Mitragotri S, Langer R. Current Status and Futyre Potential of Transdermal Drug Delivery. Nature Reviews, Drug Discovery, 2004; (3):115-124.
5. Hoar TP, Schulman JH, Transparent Water- In-Oil Dispersions, The Oleopathic Hydro-Micelle, Nature, 1943: 152; 102-103.
6. Schulman, J.H, Stoeckenius, W Prince, L.M, Mechanism Of Formation and Structure Of Microemulsions By Electron Microscopy, J. Phys. Chem, 1959: 63,1677-1680.
7. Vyas SP, Khar RK. Submicron Emulsions in Targeted and Controlled Drug Delivery, Novel Carrier System; Cbs Publishers and Distributors, New Delhi, 2002:(282-302).
8. Jadhav KR. et al., Applications Of Microemulsion Based Drug Delivery System. Curr Drug Deliv, 2006; 3(3):267-73.
9. Cordero J, Alarcon L, Escribano E, Obach R, Domenech J. A Comparative Study Of The Transdermal Penetration Of A Series Of Nonsteroidal AntiInflammatory Drugs, J. Pharm. Sci, 1997, 86:503–508.
10. Prince L M, Microemulsions. In: Lissant KJ (Ed), Emulsions And Emulsion Technology,New York : Marcel Dekker; 1974: 125-178.
11. Delgado-Charro MB, Iglesias-Vilas G, Blanco-Mendez J, Lopez QM, Marty Jp, Guy RH. Delivery Of A Hydrophilic Solute Through The Skin From Novel Microemulsion Systems. Eur J Pharm Biopharm 1997; 43: 37-42.
12. Celebi N, Kıslal O, Tarımcı N. The Effect of B- Cyclodextrin And Penetration Additives On The Release Of Naproxen From Ointment Bases. Pharmazie 1993; 48: 914-9179, Gasco M R, Gallarate M, Trotta M, Bauchiero L, Gremmo E, Chiappero O, J. Pharm. Biomed,1989; 7: 433.
13. Holmberg, K., Handbook of Applied Surface and Colloid Chemistry. 2002: Chichester, New York, Wiley.
14. Giustini MS, Murgia G, Palazzo. Does The Schulman's Titration Of Microemulsions Really Provide Meaningful Parameters? Langmuir, 2004; 20(18):7381-4
15. 15.Emsap. W.J. et al. Disperse Systems in Modern Pharmaceutics. Fourth Edition. Ed: Banker. G.S. Rhodes, C.T. Marcel Dekker Inc. New York. 2002; p260.
16. Sarkhejiya Naimish A et al. Emerging Trend of Microemulsion in Formulation and Research. International Bulletin of Drug Research. 2000; 1 (1): 54-83.
17. Kunieda H. et al. The Journal of Physical Chemistry 1988; 92: 185.
18. Park K M and Kim C K. Preparation and evaluation of flurbiprofen loaded Microemulsions for parental delivery. International Journal of Pharmaceutics 1999; 181: 173-179.
19. Peira E. and Transdermal permeation of apomorphine through hairless mouse skin from microemulsions. International Journal of Pharmaceutics 2001; 226: 47-51.
20. Rhee Y S. et al. Transdermal delivery of ketoprofen using Microemulsions. International Journal of Pharmaceutics 2001; 226: 161-170.
21. Ashok Patel and Pradeepvavia R. Preparation and In-vivo Evaluation of Self-Microemulsifying Drug Delivery System Containing fenofibrate. The AAPS Journal 2007; 226: 344-352.
22. Peltola S. et al. Microemulsions for topical delivery of estradiol. International Journal of Pharmaceutics 2003; 254: 99-107.
23. Constantinides PP. et al. Formulation and intestinal absorption enhancement evaluation of water-in-oil microemulsions incorporating medium-chain glycerides. Pharmaceutical Research 1994; 11: 13 85–90.
24. Constantinides PP. et al. Water-in-oil microemulsions containing medium-chain fatty acids/salts: formulation and intestinal absorption enhancement evaluation. Pharmaceutical Research 1996; 13(2): 205–105.
25. Jadhav. K.R. et al. Design and Evaluation of Microemulsion Based Drug Delivery System. International Journal of Advances in Pharmaceutical Sciences. 2010; 1: 156-166.
26. Brime B. et al. Amphotericin B in oil-water lecithin-based microemulsions: formulation and toxicity evaluation. Journal Pharmaceutical Sciences 2002; 91(4): 1178–85.
27. Thakker K D. and Chern W H. Development and Validation of In Vitro Release Tests for Semisolid Dosage Forms - Case Study. Dissolution Technologies 2003; 15: 10-15.
28. Shaikh I M. et al. Topical delivery of aceclofenac from lecithin organogels: preformulation study. Current Drug Delivery 2006; 3(4): 1727.
29. Tomsic M. et al. Water–Tween 40®/Imwitor 308®–isopropyl myristate microemulsions as delivery systems for ketoprofen: Smallangle Xray scattering study. International Journal of Pharmaceutics 2006; 327: 170– 177.
30. Martin A. Coarse Dispersions In: Physical Pharmacy. Fourth Edition. B.I. Waverly Pvt. Ltd. New Delhi. 1994; p495
31. 31.Giustini M. et al. Microstructure and dynamics of the water-in-oil CTAB/n-pentanol/nhexane/water microemulsion: spectroscopic and conductivity study. Journal Physical Chemistry1996; 100: 3190 3198.

32. Hsiu-O Ho. et al. Preparation of microemulsions using polyglycerol fatty acid esters as surfactant for the delivery of protein drugs. Journal of Pharmaceutical Sciences 1996; 85: 138-143.
33. Corswant C. et al. Triglyceride –based microemulsion for intravenous administration of sparingly soluble substances. Journal of Pharmaceutical Sciences 1998; 87: 200-208.
34. Dreher F. et. al. Interaction of a lecithin microemulsion gel with human stratum corneumand its effect on transdermal transport. Journal of Controlled Release 1997; 45:131 140.
35. Lv FF. et al. Studies on the stability of the chloramphenicol in the microemulsion free of alcohols. European Journal of Pharmaceutics and Biopharmaeutics 2006; 62: 288-294.