

Review Article

MICROEMULSION: A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

Microemulsions are a thermodynamically stable isotropically clear dispersion of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant molecules. A microemulsion is considered to be a thermodynamically or kinetically stable liquid dispersion of an oil phase and a water phase, in combination with a surfactant. The dispersed phase typically comprises small particles or droplets, with a size range of 5 nm-200 nm, and has very low oil/water interfacial tension. Microemulsions are clear, transparent, thermodynamically stable dispersions of oil and water, stabilized by an interfacial film of surfactant frequently in combination with a co-surfactant. Recently, there has been a considerable interest for the microemulsion formulation, for the delivery of hydrophilic as well as lipophilic drug as drug carriers because of its improved drug solubilisation capacity, long shelf life, easy of preparation and improvement of bioavailability. In this present review, we discuss about the various advantages of microemulsion in pharmaceuticals, along with its preparation, evaluation and research work carried out on microemulsions. Microemulsions are optically isotropic and thermodynamically stable liquid solutions of oil, water and amphiphile. Microemulsions are readily distinguished from normal emulsions by their transparency, low viscosity and more fundamentally their thermodynamic stability. Drug delivery through microemulsions is a promising area for continued research with the aim of achieving controlled release with enhanced bioavailability and for drug targeting to various sites in the body.

Key words: Microemulsions, Preparation and Characterization of microemulsions, research work on microemulsions.

INTRODUCTION

The term "*microemulsion*" refers to a thermodynamically stable isotropically clear dispersion of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant molecules. A microemulsion is considered to be a thermodynamically or kinetically stable liquid dispersion of an oil phase and a water phase, in combination with a surfactant. The dispersed phase typically comprises small particles or droplets, with a size range of 5 nm-200 nm, and has very low oil/water interfacial tension. Because the droplet size is less than 25% of the wavelength of visible light, microemulsions are transparent. The microemulsion is formed readily and sometimes spontaneously, generally without high-energy input. In many cases a cosurfactant or cosolvent is used in addition to the surfactant, the oil phase and the water phase. Three types of microemulsions are most likely to be formed depending on the composition:

Oil in water microemulsions wherein oil droplets are dispersed in the continuous aqueous phase

Water in oil microemulsions wherein water droplets are dispersed in the continuous oil phase;

Bi-continuous microemulsions wherein micro domains of oil and water are inter dispersed within the system.

In all three types of microemulsions, the interface is stabilized by an appropriate combination of surfactants and/or co-surfactants. The key difference between emulsions and microemulsions are that the former, whilst they may exhibit excellent kinetic stability, are fundamentally thermodynamically unstable and will eventually phase separate (Shinoda and Lindman, 1987)

Microemulsions are colloidal dispersions composed of an oil phase, aqueous phase, surfactant and co-surfactant at appropriate ratios. Unlike coarse emulsions micronized with external energy microemulsions are based on low interfacial tension. This is achieved by adding a cosurfactant, which leads to spontaneous formation of a thermodynamically stable microemulsion. The droplet size in the dispersed phase is very small, usually below 140 nm in diameter, which makes the microemulsions transparent liquids (Tenjarla, 1999).

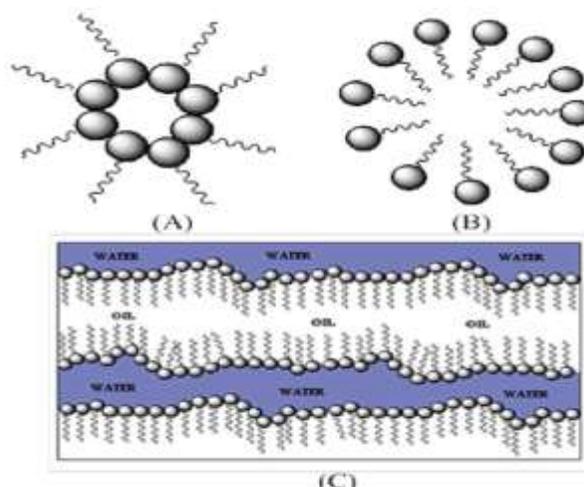


Figure 1: Micro Emulsion

In principle, microemulsions can be used to deliver drugs to the patients via several routes, but the topical application of microemulsions has gained increasing interest. The three main factors determining the transdermal permeation of drugs are the mobility of drug in the vehicle, release of drug from the vehicle, and permeation of drug into the skin (Ktistis and Niopas, 1998). These factors affect either the thermodynamic activity that drives the drug into the skin or the permeability of drug in the skin, particularly stratum corneum. Microemulsions improve the transdermal delivery of several drugs over the conventional topical preparations such as emulsions (Kreilgaard, 2000) and gels (Gasco *et al*, 1991). Mobility of drugs in microemulsions is more facile (Kriwet, Müller-Goymann, 1995), as compared to the microemulsion with gel former which will increase its viscosity and further decrease the permeation in the skin (Trotta, 1999). The superior transdermal flux from microemulsions has been shown to be mainly due to their high solubilization potential for lipophilic and hydrophilic drugs. This generates an increased thermodynamic activity towards the skin (Alvarez-Figueroa and Blanco-Méndez, 2001). Microemulsions may affect the permeability of drug in the skin. In this case, the components of microemulsions serve as permeation enhancers. Several compounds used in microemulsions have been reported to improve the transdermal

permeation by altering the structure of the stratum corneum. For example, short chain alkanols are widely used as permeation enhancers (Pershing *et al*, 1990; Liu *et al.*, 1991; Kim *et al.*, 1992). It is known that oleic acid, a fatty acid with one double bond in the chain structure, perturbs the lipid barrier in the stratum corneum by forming separate domains which interfere with the continuity of the multilamellar stratum corneum and may induce highly permeable pathways in the stratum corneum (Pershing *et al.*, 1994, Tanojo *et al.*, 1997, Hadgraft, 2001). Isopropyl myristate (IPM) is used as a permeation enhancer in transdermal formulations, but the mechanism of its action is poorly understood (Goldberg-Cettina, 1995). Nonionic surfactants are widely used in topical formulations as solubilizing agents but some recent results indicate that they may affect also the skin barrier function (Fang, 2001). It is of interest to explore the effects of these components in the organized microemulsion structures. The aim of the present study was to investigate the potential of several microemulsion formulations in transdermal delivery of lipophilic drugs.

A unique attempt was made (Acharya *et al.*, 2002) to emulsify coconut oil with the help of polyoxyethylene 2-cetyl ether (Brij 52) and isopropanol or ethanol, forming stable isotropic dispersion thus paving way for use of plant and vegetable oil to be used as oil phase in microemulsion.

The surfactants used to stabilise such systems may be:

Non-ionic,
Zwitterionic,
Cationic, Anionic surfactants

A combination of these, particularly ionic and non-ionic, can be very effective at increasing the extent of the microemulsion region. Examples of *non-ionics* include polyoxyethylene surfactants such as Brij 35 (C₁₂E₃₅) or a sugar esters such as sorbitan monooleate (Span 80). Phospholipids are a notable example of *zwitterionic surfactants* and exhibit excellent biocompatibility. Lecithin preparations from a variety of sources including soybean and egg are available commercially and contain diacylphosphatidylcholine as its major constituent (Attwood *et al.* 1992, Aboofazeli *et al.*, 1994, Aboofazeli and Lawrence, 1993, Shinoda *et al.*, 1991). Quaternary ammonium alkyl salts form one of the best known classes of *cationic surfactants*, with hexadecyltrimethyl ammonium bromide (CTAB), and the twin-tailed surfactant didodecylammonium bromide (DDAB) are amongst the most well known. The most widely studied *anionic surfactant* is probably sodium bis-2-ethylhexylsulphosuccinate (AOT) which is twin-tailed and is a particularly effective stabiliser of w/o microemulsions (Angelo *et al.* 1996).

Attempts have been made to rationalise surfactant behaviour in terms of the hydrophile–lipophile balance (HLB) (Carlfors *et al.*, 1991), as well as the critical packing parameter (CPP) (Israel achvilli *et al.*, 1976, Mitchell and Ninham, 1981). Both approaches are fairly empirical but can be a useful guide to surfactant selection. The HLB takes into account the relative contribution of hydrophilic and hydrophobic fragments of the surfactant molecule. It is generally accepted that low HLB (3–6) surfactants are favoured for the formation of w/o microemulsions whereas surfactants with high HLBs (8–18) are preferred for the formation of o/w microemulsion systems. Ionic surfactants such as sodium dodecyl sulphate which have HLBs greater than 20, often require the presence of a cosurfactant to reduce their effective HLB to a value within the range required for microemulsion formation. In contrast, the CPP relates the ability of surfactant to form particular aggregates to the geometry of the molecule itself. In most cases, single-chain surfactants alone are unable to reduce the oil /water interfacial tension sufficiently to enable a microemulsion to form, a point made in a number of pertinent microemulsions reviews (Bhargava *et al.*, 1987, Attwood, 1994, Eccleston, 1994, Lawrence, 1994, Lawrence, 1996). Medium chain length alcohols which are commonly added as cosurfactants, have the effect of further reducing the interfacial tension, whilst increasing the fluidity of the

interface thereby increasing the entropy of the system (Attwood, 1994, Eccleston, 1994). Medium chain length alcohols also increase the

mobility of the hydrocarbon tail and also allow greater penetration of the oil into this region.

Table 1: Research Work carried out on Microemulsions

Drug Name	Route	Purpose/Result
Flurbiprofen^[31]	Parenteral	Increased the solubility
Ketoprofen^[32]	Transdermal	Enhancement of permeability
Piroxicam^[33]	Oral	Increased the Solubility
Chloramphenicol^[34]	Ocular	Increased the solubility

PREPARATION OF MICROEMULSION

The drug is dissolved in the lipophilic part of the microemulsion i.e Oil and the water phases can be combined with surfactant and a cosurfactant is then added at slow rate with

RESEARCH WORK CARRIED OUT ON MICROEMULSIONS

gradual stirring until the system is transparent. The amount of surfactant and

cosurfactant to be added and the percent of oil phase that can be incorporated shall be determined with the help of pseudo-ternary phase diagram. Ultrasonicator can finally be used so to achieve the desired size range for dispersed globules. It is then allowed to equilibrate.

Gel may be prepared by adding a gelling agent to the above microemulsion. Carbomers (crosslinked polyacrylic acid polymers) are the most widely used gelling agent (Aboofazeli and Lawrence, 1993).

CONSTRUCTION OF PHASE DIAGRAM

Pseudo-ternary phase diagrams of oil, water, and co-surfactant/surfactants mixtures are constructed at fixed cosurfactant/surfactant weight ratios. Phase diagrams are obtained by mixing of the ingredients, which shall be pre-weighed into glass vials and titrated with water and stirred well at room temperature. Formation of monophasic/ biphasic system is confirmed by visual inspection. In case turbidity appears followed by a phase separation, the samples shall be considered as biphasic. In case monophasic, clear and transparent mixtures are visualized after stirring, the samples shall be marked as points in the phase diagram. The area covered by these points is considered as the microemulsion region of existence.

CHARACTERIZATION OF MICROEMULSION

The droplet size, viscosity, density, turbidity, refractive index, phase separation and pH measurements shall be performed to characterize the microemulsion.

The droplet size distribution of microemulsion vesicles can be determined by either light scattering technique or electron microscopy. This technique has been advocated as the best method for predicting microemulsion stability.

Dynamic light-scattering measurements.

The DLS measurements are taken at 90° in a dynamic light-scattering spectrophotometer which uses a neon laser of wavelength 632 nm. The data processing is done in the built-in computer with the instrument.

Polydispersity

Studied using Abbe refractometer.

Phase analysis

To determine the type of microemulsion that has formed the phase system (o/w or w/o) of the microemulsions is determined by measuring the electrical conductivity using a conductometer.

Viscosity measurement

The viscosity of microemulsions of several compositions can be measured at different shear rates at different temperatures using Brookfield type rotary viscometer. The sample room of the instrument must be maintained at $37 \pm 0.2^\circ\text{C}$ by a thermobath, and the samples for the measurement are to be immersed in it before testing.

In Vitro Drug Permeation Studies

Determination of permeability coefficient and flux

Excised human cadaver skin from the abdomen can be obtained from dead who

have undergone postmortem not more than 5 days ago in the hospital. The skin is stored at 4C and the epidermis separated. The skin is first immersed in purified water at 60C for 2 min and the epidermis then peeled off. Dried skin samples can be kept at -20C for later use. Alternatively the full thickness dorsal skin of male hairless mice may be used. The skin shall be excised, washed with normal saline and used.

The passive permeability of lipophilic drug through the skin is investigated using Franz diffusion cells with known effective diffusional area. The hydrated skin samples are used. The receiver compartment may contain a complexing agent like cyclodextrin in the receiver phase, which shall increase the solubility and allows the maintenance of sink conditions in the experiments. Samples are withdrawn at regular interval and analyzed for amount of drug released.

In Vivo Studies

Bioavailability studies: Skin bioavailability of topical applied microemulsion on rats

Male Sprague–Dawley rats (400–500 g), need to be anesthetized (15 mg/kg pentobarbital sodium i.p.) and placed on their back. The hair on abdominal skin shall be trimmed off and then bathed gently with

distilled water. Anesthesia should be maintained with 0.1-ml pentobarbital (15 mg/ml) along the experiment. Microemulsions must be applied on the skin surface (1.8 cm²) and glued to the skin by a silicon rubber. After 10, 30 and 60 min of in vivo study, the rats shall be killed by aspiration of ethyl ether. The drug exposed skin areas shall be swabbed three to four times with three layers of gauze pads, then bathed for 30 s with running water, wiped carefully, tape-stripped (X10 strips) and harvested from the animals.

Determination of residual drug remaining in the skin on topical administration.

The skin in the above permeation studies can be used to determine the amount of drug in the skin. The skin cleaned with gauze soaked in 0.05% solution of sodium lauryl sulfate and shall bathed with distilled water. The permeation area shall be cut and weighed and drug content can be determined in the clear solution obtained after extracting with a suitable solvent and centrifuging.

Pharmacological Studies

Therapeutic effectiveness can be evaluated for the specific pharmacological action that the drug purports to show as per stated guidelines.

Estimation Of Skin Irritancy

As the formulation is intended for dermal application skin irritancy should be tested. The dorsal area of the trunk is shaved with clippers 24 hours before the experiment. The skin shall be scarred with a lancet. 0.5 ml of product is applied and then covered with gauze and a polyethylene film and fixed with hypoallergenic adhesive bandage. The test be removed after 24 hours and the exposed skin is graded for formation of edema and erythema. Scoring is repeated a72 hours later. Based on the scoring the formulation shall be graded as ‘non-irritant’, ‘irritant’ and ‘highly irritant’.

Stability Studies

The physical stability of the microemulsion must be determined under different storage conditions (4, 25 and 40 °C) during 12 months. Fresh preparations as well as those that have been kept under various stress conditions for extended period of time is subjected to droplet size distribution analysis. Effect of surfactant and their concentration on size of droplet is also be studied (Aboofazeli and Lawrence, 1993, Lawrence, 1991, Lawrence, 1994)

REFERENCES

Aboofazeli, R., Lawrence, C.B., Wicks, S.R., Lawrence, M.J., (1994). Investigations into the formation and characterisation of

phospholipid microemulsions. III. Pseudo-ternary phase diagrams of systems containing water–lecithin–isopropyl myristate and either an alkanolic acid, amine, alkanediol, polyethylene glycol alkyl ether or alcohol as cosurfactant, *Int. J. Pharm.* 111: 63–72.

Aboofazeli, R. and Lawrence, M.J. (1993). 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.* 93: 161–175.

Acharya, S. P., Moulik, S. K. Sanyal, Mishra, B. K. and Puri, P. M., (2002). Physicochemical investigations of Microemulsification of Coconut Oil and Water Using Polyoxyethylene 2-Cetyl Ether (Brij 52) and Isopropanol or Ethanol. *Journal of Colloid and Interface Science*, 245: 163–170.

Alvarez-Figueroa, M.J. and Blanco-Méndez, J. (2001). Transdermal delivery of methotrexate: iontophoretic delivery from hydrogels and passive delivery from microemulsions. *Int. J. Pharm.* 215, 57–65.

Angelo, M.D., Fioretto, D., Onori, G., Palmieri, L. and Santucvelocity, A. (1996). Dynamics of water-containing sodium bis(2-ethylhex-yl)sulfosuccinate (AOT) reverse

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- micelles: a high-frequency dielectric study. *Phys. Rev. E.* 54: 993–996.
- Attwood, D., Mallon, C. and Taylor, C.J. (1992). Phase studies of oil-in water phospholipid microemulsions, *Int. J. Pharm.* 84: R5–R8.
- Attwood (1994). Microemulsions, in: J. Kreuter (Ed.), *Colloidal Drug Delivery Systems*, Dekker, New York, 31–71.
- Bhargava, H.N., Narurkar, A. and Lieb, L.M. (1987). Using microemulsions for drug delivery. *Pharm. Tech.* 11: 46–52.
- Carlfors, J., Blute, I. and Schmidt, V. (1991). Lidocaine in microemulsion - a dermal delivery system, *J. Disp. Sci. Technol.* 12: 467–482.
- Eccleston, J. (1994). Microemulsions, in: J. Swarbrick, J.C. Boylan (Eds.), *Encyclopedia of Pharmaceutical Technology*, Marcel Dekker, New York, 375–421.
- Fang, J.Y., Yu, S.Y., Wu, P.C., Huang, Y.B. and Tsai, Y.H., (2001). In vitro skin permeation of estradiol from various proniosome formulations. *Int. J. Pharm.* 215, 91–99.
- Gasco, M.R., Gallarate, M. and Pattarino, F. (1991). In vitro permeation of azelaic acid from viscosized microemulsions. *Int. J. Pharm.* 69: 193–196.
- Goldberg-Cettina, M., Liu, P., Nightingale, J. and Kurihara-Bergstrom, T. (1995). Enhanced transdermal delivery of estradiol in vitro using binary vehicles of isopropyl myristate and short-chain alkanols. *Int. J. Pharm.* 114: 237–245.
- Hadgraft, J. (2001). Skin, the final frontier. *Int. J. Pharm.* 224, 1–18.
- Israelachvilli, J.N., Mitchell, D.J. and Ninham, B.W. (1976). Theory of self assembly of hydrocarbon amphiphiles into micelles and bilayers, *J. Chem. Soc. Faraday Trans.* 72: 1525–1567.
- Kim, Y.H., Ghanem, A.H., Mahmoud, H. and Higuchi, W.I. (1992). Short chain alkanols as transport enhancers for lipophilic and polar/ionic permeants in hairless mouse skin: mechanism(s) of action. *Int. J. Pharm.* 80: 17–31.
- Kreilgaard, M., Pedersen, E.J. and Jaroszewski, J.W. (2000). NMR characterization and transdermal drug delivery potential of microemulsion systems. *J. Control. Release* 69: 421–433.
- Kriwet, K. and Müller-Goymann, C.C. (1995). Diclofenac release from phospholipid drug systems and permeation through excised human stratum corneum. *Int. J. Pharm.* 125: 231–242.
- Ktistis, G. and Niopas, I., 1998. A study on the in-vitro percutaneous absorption of propranolol from disperse systems. *J. Pharm. Pharmacol.* 50: 413–418.

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- Lawrence, M.J. (1994). Surfactant systems: microemulsions and vesicles as vehicles for drug delivery. *Eur. J. Drug Metab. Pharmacokinet.* 3: 257-269.
- Lawrence, M.J. (1996). Microemulsions as drug delivery vehicles. *Curr. Opin. Colloid Interface Sci.* 1: 826–832.
- Liu, P., Kurihara-Bergstrom, T. and Good, W.R. (1991). Cotransport of estradiol and ethanol through human skin in vitro: understanding the permeant/enhancer flux relationship. *Pharm. Res.* 8: 938–944.
- Mitchell, D.J. and Ninham, B.W. (1981). Micelles, vesicles and microemulsions, *J. Chem. Soc.* 77: 601–629.
- Pershing, L.K., Parry, G.E. and Lambert, L.D. (1993). Disparity of in vitro and in vivo oleic acid-enhanced b-estradiol percutaneous absorption across human skin. *Pharm. Res.* 10: 1745– 1750.
- Pershing, L.K., Lambert, L.D. and Knutson, K., (1990). Mechanism of ethanol-enhanced estradiol permeation across human skin in vivo. *Pharm. Res.* 7: 170–175.
- Shinoda, K. and Lindman, B. (1987). Organised surfactant systems: microemulsions. *Langmuir.* 3: 135–149.
- Shinoda, K., Araki, M., Sadaghiani, A., Khan, A. and Lindman, B. (1991). Lecithin-Based Microemulsions: Phase Behaviour and Micro-Structure. *J. Phys. Chem.* 95: 989–93.
- Tenjarla SN. (1999). Microemulsions: An overview and pharmaceutical applications. *Critical Reviews™ in Therapeutic Drug Carrier Systems* 16: 461–521.
- Trotta, M. (1999). Influence of phase transformation on indomethacin release from microemulsions. *J. Control. Release* 60: 399–405.
- Tanojo, H., Junginger, H.E. and Boddé, H.E., 1997. In vivo human skin permeability enhancement by oleic acid: transepidermal water loss and Fourier-transform infrared spectroscopy studies. *J. Control. Release.* 47, 31–39.