REVIEW ARTICLE

Topical non steroidal anti *inflammatory* drug (NSAIDs) microemulsions: Rationale, review and future prospective

Vinod Singh, Hitesh Sharma, Ram Veerma, Athar Javed[1], Mamta Singh

Department of Pharmacy, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research, Dehradun, [1]Shoolani University, Solan, India

Microemulsions serve as ideal candidates as potential drug delivery system due to their specialized qualities of improved solubilisation of drug, extended shelf life and ease of method of preparation and administration to patients. The unique features of microemulsions are thermodynamically stable, clear, colloidal dispersion of water and oil that are stabilized by surfactant and cosurfactant. Microemulsion typically has a droplet diameter of approximately 100 nm or less. Microemulsions have numerous applications in pharmaceutics and many other industries. In the present review we shall discuss about the various aspects of microemulsion with respect to the field of non steroidal anti *inflammatory* drug, along with its preparation, evaluation and research work carried out in microemulsion.

Key words: *Droplet size, microemulsion, solubility, surfactant*

INTRODUCTION

Topical drug delivery systems have become a major class in the pharmaceutical sector. Although this route was discovered earlier, but still discoveries in this field are continuously coming into existence. The purpose of topical dosage forms is to conveniently deliver drugs to a localized area of the skin.[1] Topical medications are applied directly on the painful body area, where they penetrate the skin. A topical medication's site of activity is in the peripheral tissues, including soft tissue and peripheral nerve, directly underlying the site of application. Topical drugs formulated as a gel, microemulsion, cream, liquid, or patch, should not produce any clinically significant systemic drug concentration. Transdermal medications, on the other hand, are also applied directly to the skin, but the site of drug application can be distant from the area of pain. Transdermal drugs sites of activity are not local but via a systemic effect.

Colloidal drug delivery of non steroidal anti *inflammatory* drug's (NSAIDs) provide efficient delivery by the use of "microemulsion." Microemulsions were first introduced by Hoar and Schulman in 1943.[2] They are thermodynamically stable, low viscosity homogenous, isotropic systems in which two immiscible liquids (i.e., water and oil) are mixed leading to the formation of a single phase by means of an appropriate surfactant and co-surfactant.

Thus, microemulsion formation takes place spontaneously, with an average droplet diameter of 10-140 nm.[3] Microemulsion are having the ability of solubilizing the poorly water soluble drugs by the virtue of its small droplet size, their composition and structure enable them to incorporate a greater amount of drug than other conventional topical formulations such as ointments, creams, gels and lotions.

A definite boundary exists between oil and water phases over which surfactant are located. The short to medium-chain alcohols are generally considered as co-surfactants in the microemulsion system. The surfactant and co-surfactant play the role of lowering

Address for correspondence:
Dr. Vinod Singh,
Department of Pharmacy, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research, Balawala, Dehradun, Uttarakhand, India.
E-mail: vinod.panipat@gmail.com

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the interfacial tension of the system. Conventional surfactant molecules comprised polar head group region and non-polar tail region. The existence of micro-domains of different polarity within the same single-phase solution enables both hydrophilic and lipophilic drugs to be solubilized. The unique property of microemulsion for increased solubility of drugs makes NSAIDs a suitable candidate for the topical delivery.

Non-steroidal anti-inflammatory drugs are the most popular and most widely used drugs for the treatment of pain, inflammation, and are the choice of drugs for the treatment of various types of arthritis. They are *Cyclooxygenase*-2 (Cox-2) inhibitor with inhibit prostaglandin synthesis responsible for inflammation. Majority of NSAIDs are administered orally and due to the adverse effects associated with the orally administered NSAIDs, such as gastric and duodenal irritation. Therefore, by the use of microemulsion as topical delivery system for the delivery of NSAIDs, several other toxicities such as nausea, vomiting and diarrhea caused to the high concentration of NSAIDs in the alimentary canal can also be avoided. The use of NSAIDs topically prevents dose related adverse effects of such as acute renal insufficiency and prostaglandin inhibition. Numerous other advantages of topically administered NSAIDs include higher concentration at the desired site that blood levels, increased permeation of drugs through the stratum corneum, absence of gastric degradation and hepatic first pass effect and lastly as it is administered topically it does not require any professional supervision and nor does it have the stigma associated needles as compared to parental dosage form.[4] Therefore, microemulsion serves as an ideal delivery system for the delivery of NSAIDs.

ADVANTAGES OF MICROEMULSION

The advantages of microemulsion for the topical delivery of drugs:[5-9]

1. The increased thermodynamic activity of the drug may favor it's partitioning into the skin, by favoring drug diffusion.
2. The ingredients of microemulsion may reduce the diffusional barrier of the stratum corneum and increase the permeation rate of drug via skin by acting as permeation enhancers and "super solvents" of drug.
3. Good thermodynamically stable and inexpensive.
4. It is used as a vehicle for topical and transdermal applications, to enhance the bioavailability for poorly water soluble drug.
5. It acts as "super solvents" of drug. They can solubilize both hydrophilic and lipophilic drugs, including drugs that are relatively insoluble in both aqueous and hydrophobic solvents.
6. Microemulsions are having wide applications in colloidal drug delivery systems for the purpose of drug targeting and controlled release.[10]
7. It is a better drug delivery system as compared to other drug delivery systems [Table 1].

Table 1: Comparative study among various delivery systems

Various colloidal delivery system[17]		
Delivery system	**Advantages**	**Disadvantages**
Micelles	Low viscosity, small droplet size, easy preparation long shelf life	Low solubilisation potential toxicity of surfactant
Microemulsions	High solubility of drug, small droplet size easy preparation long shelf life	Large amount of surfactant drug solubility affected potential toxicity of surfactant
Emulsions	Less surfactant high solubility drug-carrie	High viscosity instability large droplets, short shelf life
Liposomes	Composition-lecithin-cholesterol	Difficult to prepare and control size high viscosity
Nanoparticles	Long storage life, slow degradation in body	Polymers are not bio-acceptable

DISADVANTAGES OF MICROEMULSION

1. The major drawback with a microemulsion application is a high concentration and a narrow range of physiologically acceptable surfactants and cosurfactants.[11,12]
2. It has limited potential in topical application due to their toxic and irritant properties of components of the microemulsion.
3. The low viscosity of microemulsion restrains its clinical application due to inconvenient use.
4. Microemulsion stability is influenced by environmental parameters such as temperature and ph.
5. NSAIDs, delivered by the use of microemulsion share constraining characteristics such as low molecular mass of the drug (<500 da), high lipophilicity of the drug (log *P* in the range of 1-3, where log *P* = 1 means 10:1 organic: Aqueous), low melting point (<200°C) and high potency (dose is <50 mg per day),[13-16] therefore, the drug must be potent enough to reach the site in appropriate quantity at the site of action.
6. Topical preparations are concerned with the medicaments applied to the surface of a part of the body and have pharmacological effects only in a specific area of the body and are formulated in such a manner aiming that the systemic absorption of the medicament is minimal. NSAID administered topically penetrate slowly and in small quantities into the systemic circulation; compared with equivalent oral administration, the bioavailability and maximal plasma NSAID concentration after topical application are generally less than 5 and 15%, respectively, as compared to oral administration, NSAID achieves a higher concentration in dermis when applied topically.

MECHANISM OF DRUG TRANSPORT

As per the dermal application, microemulsion tend to increase the transdermal permeation of drugs as a result of interaction with stratum corneum, changing the structural rearrangement of its lipid layers and altering the partition coefficient of the drug towards the skin thereby act as a penetration enhancer. There is an increase in the concentration gradient and increased thermodynamic activity towards the skin. Those drugs candidate that have a sufficient hydrophilic lipophilic characteristic can permeate through the lipid bilayer directly by passive diffusion. Drugs having limited lipid solubility are transported via carrier mediated mechanism through the lipid bilayer [Figure 1].

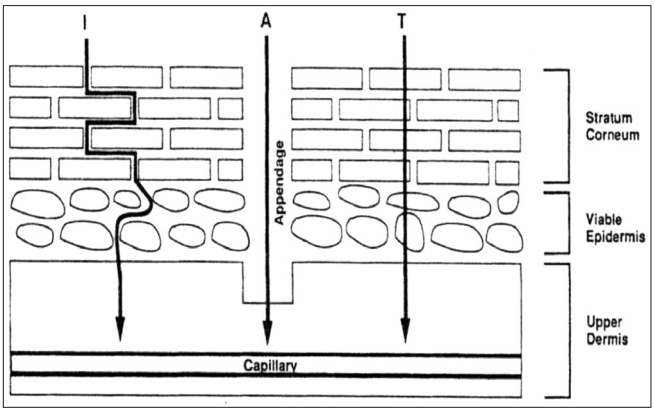

Figure 1: Diagram of the potential routes of drug penetration - stratum corneum. I = Intercellular, T = Transcellular, A = Appendegeal

FACTORS AFFECTING PENETRATION OF DRUG THROUGH THE SKIN

The nature of the drug (hydrophilic or lipophilic drug)-generally lipophilic NSAIDs e.g., ketoprofen, indomethacin, piroxicam are preferred more since the stratum corneum in lipophilic in nature, hydrophilic drugs permeate very slowly through the stratum corneum due to its inability to partition from the aqueous environment to the lipophilic environment. Therefore, NSAIDs that have a high partition coefficient are preferred for topical delivery.

The nature of the vehicle (gel-state, emulsions, microemulsions, complexation of the drug with cyclodextrines, liposomes and nanoparticles)-in a gel state the active constituent in entrapped with the three dimensional polymeric matrix, the release is dependent on the nature of matrix and the concentration of polymer. However, additional components such as penetration enhancer must be added into the gel to facilitate the permeation of the active component through the skin. Microemulsion have an inherent property of increased solubility of hydrophilic and lipophilic drug and an increased permeation through the skin and decreased particle size as compared to emulsion making them an ideal candidate for topical application. Cyclodextrin on the other hand, have a hydrophilic exterior and a lipophilic core, making it a suitable candidate for poorly soluble lipophilic drugs, however if used for topical delivery, its hydrophilic core makes it unsuitable to permeate through the stratum corneum. Liposomes are microscopic vesicles consisting of one or more membrane-like phospholipid bilayers surrounding an aqueous medium.[18,19] Liposomes are insoluble in water and cannot penetrate the skin deeply rendering them unsuitable for topical application. Nanoparticles have attained limited success in topical delivery considering their deep penetration and toxicity property.

Presence of the enhancers (isopropyl myristat, isopropyl palmitat, hydrogenated soybean phospholipids, non-ionic surfactants, terpenes, alcohols with long carbon chain c8-c12, etc.,) this tends to increase the penetration of the drug across the skin.

ESSENTIAL CONDITIONS FOR FORMATION OF MICROEMULSION

Few essential condition that has been described by Schulman, *et al.*,[2] are as follows:

1. The production of a very low interfacial tension at the water-oil interface;
2. The formation of a highly fluid interfacial surfactant film
3. The penetration and association of the molecules of the oil phase with the interfacial surfactant film.

PSEUDOTERNARY PHASE DIAGRAM AND STRUCTURE OF MICROEMULSION

The purpose of constructing pseudo ternary phase diagrams was to obtain the concentration ranges of the predetermined components of oil, surfactant and the aqueous phase that can result in large existence area of microemulsion. Co-surfactants are used at a fixed ratio to the surfactant and are treated as a pseudo component. Gibbs phase diagrams can be used to show the influence of changes in the volume fractions of the different phases on the phase behavior of the system.[20] The apex of the triangles represents 100% of the particular component of the microemulsion, as we move away from the apex the concentration of the particular component decreases and increases the concentration of the other two components. Each point, within the pseudo ternary phase diagram, represents an unique composition of oil, surfactant or co-surfactant and water. Each mixture was visually observed for phase clarity and flow ability. These values were then used to determine the boundaries of the microemulsion domain corresponding to the chosen value of oils, as well as the surfactant or co-surfactant mixing ratio.

A wide variety of structures and phases of microemulsion are formed by the mixture of oil, water and surfactants [Figure 2]. The structural examinations of the microemulsion can reveal the existence of regular emulsions, anisotropic crystalline hexagonal or cubic phases, and lamellar structures depending on the ratio of the components.

CONSTITUENTS OF MICROEMULSION

Oil phase

The oil component influences curvature by its ability to penetrate and hence swell the tail group region of the surfactant monolayer. Saturated and unsaturated fatty acids, long chain alcohols, triglycerides, e.g., toluene, cyclo hexane, mineral or vegetable oil, silicone oil, or esters of fatty acids, etc., are widely used as oil component.

Aqueous phase

The aqueous phase may contain hydrophilic active ingredients and preservatives. Buffer solutions are used as aqueous phase by some researchers.

Surfactants

The hydrophilic-lipophilic balance (HLB) system has been used for the selection of surfactants for microemulsion. Using this system, w/o microemulsion are formed using emulsifiers within the HLB range of 3-6, while o/w microemulsion are formed within the range of 8-18. The choice of emulsifiers is determined by the average HLB requirement of the proposed microemulsion.[21,22] The surfactant are generally ionic, non-ionic or amphoteric due to their inherent property of lower toxicity, lower potential for irritation and good cutaneous tolerance. The surfactants chosen are generally from the non-ionic group because of their good cutaneous tolerance.

Co-surfactants

In most cases, single-chain surfactants alone are unable to reduce the o/w interfacial tension sufficiently to enable a microemulsion to form.[23,24] The presence of co-surfactants allows the interfacial film sufficient flexibility to take up different curvatures required to form microemulsion over a wide range of composition.[25-27] The co-surfactant, generally used were short chain fatty alcohol such as pentane, hexanol, benzyl alcohol. these are most often polyols, esters of polyols derivatives of glycerol and organic acids, poloxamer, polysorbate 80, span 20, cinnamicaldehyde, alcohol, (ethanol, propanol, isopropanol, propylene glycol etc.,), long chain alcohols (1-buthanol, decanol, octanol etc.,).[28] Their main purpose is to make the interfacial film fluid by wedging themselves between the surfactant molecules.[29]

SOLUBILISING PROPERTY OF MICROEMULSIONS

Achieving good solubility is one of the important criteria for the formation of efficient pharmaceutical formulations. It is well known that only the fraction of the drug that is dissolved in the vehicle can permeate through the skin. Since the release of drug for the formulation is dependent on the concentration (activity) gradient, thus microemulsion serves as an advantage. Research indicated that the unique structural organization of the phases in microemulsion contribute to additional solubility regions, increasing the load capacity of the microemulsion, compared to non-structured solutions

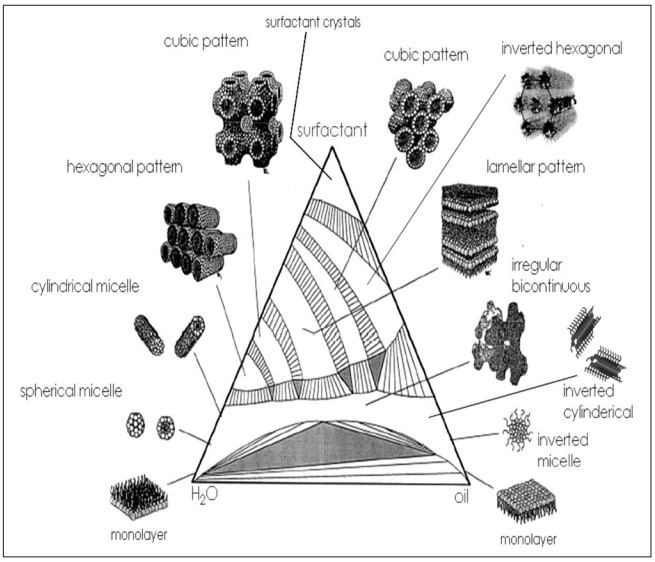

Figure 2: Phase diagram: Water (aqueous phase), oil, surfactant and formation of structure of microemulsion

containing the same fraction of the constituents, which principally can form microemulsion.[30-33] Microemulsions are having a capability of incorporating a large variety of lipophilic and hydrophilic phases. The increased solubility of the drug in the microemulsion is by the virtue of the increase in the additional solubilization sites of the lipophilic and hydrophilic moiety of the surfactant interface film formed in the microemulsion.

METHOD OF PREPARATION

While formulating microemulsion, three factors must be considered.[34]

Firstly, emulsifiers or surfactants must be selected to produce an ultra-low interfacial tension ($<10^{-3}$ mn/m). Low interfacial tension is the prime reason for spontaneous emulsification of oil in water and water in oil.

Secondly, concentration of emulsifier or surfactant must be high to provide the number of surfactant molecules needed to stabilize the micro droplets produced by ultra-low interfacial tension. Microemulsion are in the range of 100-1000 A° in diameter, 30% of oil dispersed in water with 200 A° droplet diameter will create 10^6 cm^2 of total interfacial area per millimeter of microemulsion, thus the large concentration (10-40%) of surfactant is required to stabilize the newly created interface of microemulsion droplets. the right choice of structure of surfactant and co-surfactant can reduce the concentration of surfactant required for microemulsion. surfactant partitions into three compartments: Water, oil, and interface and thus minimizes their concentration in bulk oil and water phases.

Thirdly, factor to be considered is flexibility or fluidity of the

interface to promote the formation of microemulsion. Short chain alcohols (c_4-c_7) are often added as co-surfactant in surfactant, water and oil system for preparing microemulsion.

Phase titration method

Microemulsions are prepared by the spontaneous emulsification method (phase titration method) and can be depicted with the help of phase diagrams. Construction of phase diagram is a useful approach to study the complex series of interactions that can occur when different components are mixed. Microemulsions are formed along with various association structures (including emulsion, micelles, lamellar, hexagonal, cubic, and various gels and oily dispersion) depending on the chemical composition and concentration of each component. The understanding of their phase equilibria and demarcation of the phase boundaries are essential aspects of the study, as quaternary phase diagram (four component system) is time consuming and difficult to interpret. Pseudoternary phase diagram is often constructed to find the different zones including microemulsions zone, in which each corner of the diagram represents 100% of the particular component. The region can be separated into w/o or o/w microemulsion by considering the composition that is whether it is oil rich or water rich. Observations should be made carefully so that the metastable systems are not included.[35]

Phase inversion temperature method

Phase inversion of microemulsion occurs up on addition of excess of the dispersed phase or in response to temperature.[36] During phase inversion drastic physical changes occur including changes in particle size that can affect drug release both *in vivo* and *in vitro*. These methods make use of changing the spontaneous curvature of the surfactant. For the non-ionic surfactant, this can be achieved by changing the temperature of the system, forcing a transition from an o/w microemulsion at low temperature to a w/o microemulsion at higher temperature is called as transitional phase inversion. During cooling, the system crosses a point of zero spontaneous curvature and minimal surface tension, promoting the formation finely dispersed oil droplets.

Rosano[37] suggested a way to find out the minimum amount of primary surfactant needed for a particular system. The minimum amount of primary surfactant required for the microemulsion is calculated by determining the surface area or mono-molecular interfacial film area necessary to form between the dispersed phase and the continuous phase.

If V (ml) of phase is dispersed into spherical droplets of radius r (a°), the total volume of dispersed phase can be expressed as

$$V = a\ (4/3)\ \pi r^3 \quad (1)$$

Where,
a = total number of droplets formed by the dispersed phase.

The total surface area a of the droplets is $a = a4\ \pi r^2$

$$A = \delta\ n \quad (2)$$

Where δ = area per surfactant molecule
n = number of surfactant molecule.
Combining these equations

$$n = (3\ v)/\delta\ r \quad (3)$$

The value of δ can be obtained from surface tension versus log concentration plot of surfactant solution.

For microemulsion upper limit of r is 40 nm, while lower limit is decided by surfactant chain length.

Rosano calculation provides the minimum amount of surfactant necessary to cover the interface. It does not include amount of surfactant that is dispersed in both aqueous and oil phase.

EVALUATION OF MICROEMULSION

Sophisticated physical techniques such as
Small angle X-ray scattering, Small angle neutron scattering, Dynamic light scattering, Transmission electron microscopy, Nuclear magnetic resonance, Time resolved fluorescence quenching. Can be used for evaluation of microemulsion depending upon properties.

RESEARCH WORK BEING CARRIED OUT IN THE FIELD OF MICROEMULSION USING NSAIDs

In the recent years, there has been a large interest in the topical delivery of NSAIDs via various delivery systems. Various researches had been carried out for the delivery of NSAIDs via hydrogels, microemulsion, transdermal delivery system, nanoemulsion and cyclodextrin entrapped NSAIDs [Table 2].

CONCLUSION

Microemulsions serve as a promising drug delivery system for NSAID. Microemulsions provide a substantial advantage about the solubility. Several lipophilic drugs are made soluble in organic phase and then incorporated in combination of aqueous and surfactant mixture, providing a desired dosage form with therapeutic effect.

Large scale production is easy in terms of formulation time period. Microemulsion offers various advantages like increased solubility, bioavailability and controlled release. However, much work still remains to be done in the field of topical microemulsion with relation to NSAID.

Some factors should be considered while dealing with microemulsion, such as suitable type of surfactant to protect

Table 2: Research work using non steroidal anti *inflammatory* drug (NSAIDs) for topical delivery

Name of drug	Research work
Nimsulide[38]	Formulation, development and evaluation of topical microemulsion gels for nimsulide
Aceclofenac[39]	Development and characterization of microemulsion formulation for transdermal delivery of Aceclofenac: A research
Ibuprofen[40]	Fabrication and evaluation of hydrogel thickened microemulsion of ibuprofen for topical delivery
Ketoprofen[41]	Formulation and *in vitro* evaluation of ketoprofen in palm oil esters nanoemulsion for topical delivery
Ketoprofen[42]	The novel formulation design of o/w microemulsion of ketoprofen for improving transdermal absorption
Diclofenac[43]	Topical delivery of diclofenac using microemulsion systems
Indomethacin[44]	Microemulsions as vehicles for transdermal permeation of drugs
Piroxicam[45]	Fluorescence quenching of acridine orange in microemulsions induced by the non-steroidal anti-inflammatory drug piroxicam
Ketoprofen[46]	Lecithin microemulsions for the topical administration of ketoprofen: Percutaneous adsorption through human skin and *in vivo* human skin tolerability
Ketoprofen[47]	Transdermal delivery of ketoprofen using microemulsions
Piroxicam[48]	Inclusion complex of piroxicam with beta-cyclodextrin and incorporation in cationic microemulsion. *in vitro* drug release and *in vivo* topical anti-inflammatory effect
Indomethacin[49]	Influence of phase transformation on indomethacin release from microemulsions

and dissolve drug. Surfactant can be cationic, anionic, non-ionic or mixed system. Concentration of surfactant influences the carrier system because concentration of surfactant determines the effectiveness of drug delivery system. Finally the condition of target site is critically important.

Microemulsion can be a potential delivery system for the delivery of two or more medicaments simultaneously, but the main challenge is the control of drug diffusion and partitioning between dispersed phase and dispersion medium.

Ultimately, microemulsion offers a potentially powerful carrier system for drug delivery having suitable characteristics of high solubilization capacity, transparency, thermodynamic stability, and ease in preparation and high diffusion and absorption rates through layers of skin.

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