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A REVIEW ON MICROEMULSION: A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

It is suggested that microemulsion is the most effective topical preparation than its conventional skin preparations like cream and gel. They can be potential drug delivery systems for the delivery of more than one medicament simultaneously. Surfactant molecules contain both a polar as well as a polar group. So they exhibit a very peculiar behavior, firstly, they get adsorbed at the interface, where they can fulfill their dual affinity with hydrophilic groups located in aqueous phase and hydrophobic groups in oil or air. Secondly, they reduce mismatching with solvent by Micellization Process.

INTRODUCTION

The concept of microemulsion was first introduced by Hoar and Schulman in 1943.

The term "*microemulsion*" refers to a thermodynamically stable, isotropically clear dispersion of two immiscible liquids, such as oil and water, which is stabilized by an interfacial film of surfactant molecules. Surfactant molecules contain both a polar as well as an a polar group. So they exhibit a very peculiar behavior, firstly, they get adsorbed at the interface, where they can fulfill their dual affinity with hydrophilic groups located in aqueous phase and hydrophobic groups in oil or air. Secondly, they reduce mismatching with solvent by Micellization Process.

The dispersed phase typically comprises of 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 aretransparent.

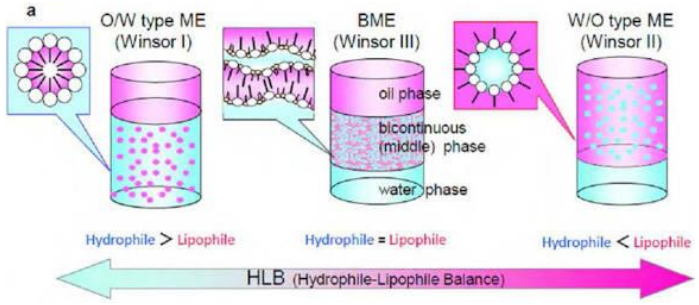
The microemulsion is formed readily and sometimes spontaneously, generally without high-energy input. In many cases a co surfactant or co solvent is used in addition to the, the oil phase and the water phase[(1)]

Types of microemulsion:- [(2)]

The three basic types of microemulsions are-

1. Oil in water (o/w) or Winsor I
2. Water in oil (w/o) or Winsor II
3. Bicontinuous microemulsions or Winsor III

In o/w microemulsions the volume fraction of oil is low conversely in w/o emulsion the volume fraction water is low and the oil droplets in o/w microemulsions are surrounded by the electrical double layer, which can extend into the external phase for a considerable distance up to 100 nm, depending up on the electrolyte concentration[(2)]



Method of preparation: - (3)

1. 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 microemulsions by simply 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.

2. Phase inversion method:-

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 microemulsions at low temperature to a w/o microemulsions 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

Advantages of microemulsion:- [4-14]

Microemulsions have several advantages which are as follows:-

1:- Microemulsions are thermodynamically stable system and allows self-emulsification of the system

2:-it is used in various pharmaceuticals and cosmetic formulations.

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 enhancers and 'supersolvents' of drug.

6:- have long shelf life.

7: It having Wide applications in colloidal drug delivery systems for the purpose of drug targeting and controlled release

8:- microemulsions are Helpful in taste masking.

9:- . Having the ability to carry both lipophilic and hydrophilic drugs

10:- Microemulsions have low viscosity compared to primary and multiple emulsions**.**

Disadvantages of microemulsion :- [4-14]

Microemulsions have several disadvantages which are as follows:-

1:-components of microemulsion are toxic and irritant in nature so it has limited topical Application.

2:-The stability of microemulsion is influenced by several environmental factors such as:-temp, Ph.These parameters change as microemulsion delivered to patients.

3:- It Require large amount of S/Cs for stabilizing droplets.

4:- It has limit potential topical application due to their toxic and irritant properties of components.

APPLICATIONS

1-Oral delivery:- **(15)**

Microemulsions have the potential to enhance the solubility of poorly soluble drugs (particularly BCS class II or class IV) and it overcome the dissolution related bioavailability problems. Due to the presence of polar, nonpolar and interfacial groups, hydrophilic drugs including macromolecules can be encapsulated with varying solubility.

These systems have been protecting the incorporated drugs against oxidation, enzymatic degradation and enhance membrane permeability.

Presently, Sandimmune Neoral(R) (Cyclosporine A), Fortovase(R) (Saquinavir), Norvir(R) (Ritonavir) etc. are the commercially available microemulsion formulations. Microemulsion formulation can be potentially useful to improve the oral bioavailability of poorly water soluble drugs by enhancing theirsolubility in gastrointestinal fluid.

2-Parenteral delivery (16)

The formulation of parenteral dosage form of lipophilic and hydrophilic drugs has proven to be difficult. O/w microemulsions are beneficial in the parenteral delivery of sparingly soluble drugs

where the administration of suspension is not required. They provide a means of obtaining relatively high concentration of these drugs which usually requires frequent administratios.

Advantages:-

1-that they exhibit a higher physical stability in plasma than liposomes or other vehicles and the internal oil phase is more resistant against drug leaching.

2- Several sparingly soluble drugs have been formulated into o/w microemulsion for parenteral delivery

3-Topical delivery (17, 18)

Topical administration of drugs can have advantages over other methods for several reasons, Reasons of advantages over other routes of administration are-

1-the avoidance of hepatic first-pass metabolism

2- Salivary and degradation of the drug in stomach and related toxicity effects.

3- The direct delivery and targetability of the drug to affected areas of the skin or eyes.

Now a day, there have been a number of studies in the area of drug penetration into the skin. They are able to incorporate both hydrophilic (5-flurouracil, apomorphine hydrochloride, diphenhydramine hydrochloride, tetracaine hydrochloride, methotrexate) and lipophilic drugs (estradiol, finasteride, ketoprofen, meloxicam, felodipine, triptolide) and enhance their permeation. Since formation of microemulsion formation requires high surfactant concentration, the skin irritation aspect must be considered especially when they are intended to be applied for a longer period.

4- Ophthalmic delivery (19,20)

In conventional ophthalmic dosage forms, water soluble drugs are delivered in aqueous solution while water insoluble drugs are formulated as suspension or ointments. Recent research has been focused on the development of new and more effective delivery systems.

Microemulsions have emerged as a promising dosage form for ocular use. Chloramphenicol, an antibiotic used in the treatment of trachoma and keratitis, in the common eye drops hydrolyzes easily. Lv *et al*. investigated the microemulsion composed of Span 20, Tween 20, isopropylmyristate and water as potential drug delivery systems for eye drops. Chlroamphenicol was entrapped in the o/wmicroemulsion free of alcohol. The formulation showed greater penetration in the eye which allowed the possibility of decreasing dosing frequency and thereby improve patient compliance.

5- Nasal delivery (21)

Recently, microemulsions are being studied as a delivery system to enhance uptake of drug through nasal mucosa. The mucoadhesive polymer helps in prolonging residence time on the mucosa. Lianly et al. investigated the effect of diazepam on the emergency treatment of status epilepticus. They found that the nasal absorption of diazepam fairly rapid at 2 mg kg-1 dose with maximum drug plasma concentration reached within 2-3 min.

6-Periodontal Delivery (22)

Periodontal disease is a collective term for a number of progressive oral pathological afflictions like inflammation and degeneration of the gums, periodontal ligaments, cementum and its supporting bone. The invention of Brodin *et al*. included a novel pharmaceutical composition comprising local anaesthetic in oil form, surfactant, water and optionally a taste masking agent.

The composition was in the form of an emulsion or microemulsion and had thermoreversible gelling properties i.e. it was less viscous at room temperature than after introduction onto a mucous membrane of a patient. The surfactant in the formulation imparted the thermoreversible gelling properties.

The surfactants used in these microemulsions are-

1-Poloxamer 188®

2- Poloxamer 407®

3-Arlatone 289®.

The composition could be used as a local anaesthetic for pain relief within the oral cavity in conjunction with periodontal scaling and root planning and overcame the problem with the existing topical products (jelly, ointment or spray) such as lack of efficacy due to inadequate depth of penetration, too short duration and difficulties in administration due to spread, taste etc.

7-Brain Targeting (23)

Intranasal administration is a simple, practical, cost effective, convenient and noninvasive route of administration for rapid drug delivery to the brain. It allows a direct transport of drugs to the brain circumventing the brain barriers.

Vyas *et al*. prepared mucoadhesive microemulsion for an antiepileptic drug clonazepam. The aim was to provide rapid delivery to the rat brain. Brain/blood ratio at all sampling points up to 8h following intranasal administration of clonazepam mucoadhesive microemulsion compared to i.v. was found to be 2-fold higher indicating larger extent of distribution of the drug in the brain.

8- Ocular and Pulmonary Delivery (24)

Microemulsions are also used in the treatment of eye diseases, drugs are essentially delivered topically. O/w microemulsions have been investigated for ocular administration, to dissolve poorly soluble drugs, to increase absorption and to attain prolong release profile.

Eg of ocular and pulmonary delivery are- **pilocarpin** which is formulated by using lecithin, propylene glycol and PEG 200 as co-surfactant and IPM as the oil phase.

Current and future prospects of microemulsion:-

During the last few decades lots of research work has been carried out on microemulsion system **(table 1)** for providing novel solutions to overcome the problems of poor aqueous solubility of highly lipophilic drug compounds and provide reproducible bioavailability from 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 Microemulsions may constitute an effective system for the delivery of both water soluble and oil soluble drugs to the ocular tissues without compromising the convenience to the patients, as well for physicians ,for adjustment of dose and dosing frequency according to the disease therapy.

Marketed formulations of microemulsion:-(table -1)

Name of Drug	Route of administration	Purpose
Apomorphine(25)	Transdermal	Increased the solubility
Ketoprofen (26)	Transdermal	Increased the permeability
Prilocainne-HCL(27)	Transdermal	Increased the solubility
Estradiol(28)	Transdermal	Improved in solubillization
Aceclofenac(29)	Dermatological	Increased the solubility
Piroxicam(30)	Oral	Increased the solubility
Diclofenac(31)	Transdermal	Permeability enhancement
Dexamethasone(32)	Topical ocular	Enhanced the bioavailability
Chloramphenicol(33)	Ocular	Increased the solubility
Ibuprofen(34)	Topical	Increasing the solubility
Glipizide(35)	Oral	Enhance drug dissolution and drug bioavailability
Hydroxy safflor yellow A (36)	Oral	Improved oral bioavailability
Aceclofenac(37)	Topical	Increasing solubilisation, patient compliance
Itraconazole(38)	Parenteral	For better absorption
Timolol(39)	Ophthalmic	For better absorption
Terbinafine(40)	Transdermal	Permeability enhancement
Fenofibrate(41)	Self-microemulsifying	Increased the solubility
Progesterone(42)	Transdermal	Increased the chemical stability
Doxorubicin(43)	Topical	Increasing the solubility

CONCLUSION

Microemulsions are commercially 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 associated increase in systemic absorption. They can be potential drug delivery systems for the delivery of more than one medicament simultaneously. Microemulsion have been shown to be able to protect labile drug, control drug release, increase drug solubility, increase bioavailability and reduce patient variability Furthermore it has proven possible to formulate preparations suitable for most routes of administration. Microemulsions may constitute an effective system for the delivery of both water soluble and oil soluble drugs to the ocular tissues without compromising the convenience to the patients as well for physician for adjustment of dose and dosing frequency according to the disease therapy..

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