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Review on Microemulsion a Novel Approach for Antifungal Drug Delivery

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ABSTRACT

Microemulsion is an best candidates as novel drug drlivery system because of their shelf life and improve the drug solubilization with easy of preparation and administration. The term microemulsion refers to thermodynamically stable iostropically dispersion of two immisible liquid such as oil and water stabilized by interfacial film of surfactant molecule. Now a days microemulsion is an emerging trade and having worldwide importance in varity of technological application .These application include enhanced oil recovery,cosmeceuticals agriculture ,metal cutting,organic and bio organic reaction.

KEYWORD: *Microemulsion, Novel approach, Antifungal drug delivery, Application*

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INRODUCTION

Micro emulsion is Dispersion made of water, oil, and surfactant(s) that is anisotropic and thermodynamically steady machine with dispersed domain diameter various about from 1 to a hundred nm, typically 10 to 50 nm.1 Micro emulsions are clear, thermodynamically stable, isotropic liquid mixtures of oil, water and surfactant, often in combination with a co surfactant. The aqueous segment may also incorporate salt(s) and/or different ingredients, and the "oil" may additionally absolutely be a complex combination of one of a kind hydrocarbons and olefins.2 The time period of micro emulsion applies to a mixture with at least three components; an oily phase, an aqueous section and a surface lively species, so known as surfactants. Sometimes the forth element i.e., co-surfactant can/must be present. (1,2)

Microemulsions containing the oil and aqueous phase, surfactant and cosurfactant (cos), are optically obvious 3,4mixtures with a very small droplet measurement (G140 nm). two Microemulsions have been growing in recognition and garnering more interest in latest years, due to the fact they may also enhance the transdermal absorption of drug molecules by using growing drug solubilities and enhancing their partition 5coef ficients. A hydrogel base is used very regularly in topical 6,7formulations. . The hydrogel system was once prepared and studied as a vehicle for its permeation practicable

Microemulsions are currently the challenge of many investigations because of their broad range of workable and real utilizations. The excessive capability of microemulsions for capsules makes them fascinating formulations for pharmaceuticals. These structures additionally offer a number of benefits for oral administration, along with increased absorption, improved clinical efficiency and reduced toxicity (3,7)

Advantages and Disadvantages of Miceoemulsion(8-10)

Advantages of microemulsion

Microemulsions exhibit various blessings as a drug delivery system

1. Microemulsions are thermodynamically secure gadget and allows self-emulsification of the system.
2. Microemulsions act as supersolvents for drug, can solubilise both hydrophilic and lipophilic drugs inclusive of drugs that are relatively insoluble in both aqueous and hydrophobic solvents.
3. The dispersed phase, lipophilic or hydrophilic (oil-in-water, O/W, or water-in-oil, W/O microemulsions) can act as a potential reservoir of lipophilic or hydrophilic drugs, respectively. Drug release with pseudo-zero-order kinetics can be obtained, depending on the volume of the dispersed phase, the partition of the drug and the transport rate of the drug.

4. The suggest diameter of droplets in microemulsion is beneath 0.22 mm. This yield a giant interfacial area, from which the drug is released swiftly into external segment when absorption (in vitro or invivo) takes place, retaining the awareness in the external phase close to initial levels.
5. Having the capability to lift both lipophilic and hydrophilic drugs.
6. Microemulsion are easy to put together and require no significant energy contribution at some point of coaching this is due to better thermodynamic stability.
7. Microemulsions have low viscosity in contrast to major and multiple emulsions.
8. The use of microemulsion as transport systems can improve the efficacy of a drug, permitting the complete dose to be reduced and thus minimizing aspect effects.
9. The formation of microemulsion is reversible. They may additionally become unstable at low or high temperature however when the temperature returns to the balance range, the microemulsion reforms.

Disadvantages of Microemulsion Based Systems:

1. Require massive amount of S/Cs for stabilizing droplets.
2. Limited solubilizing potential for high-melting elements used in the system.
3. The surfactant be unhazardous for use in pharmaceutical applications.
4. Microemulsion balance is influenced by way of environmental parameters such as temperature and pH. These parameters change as microemulsion delivered to patients.

Composition (11-24)

The major components of micro emulsion system are:

1. Oil phase
2. Surfactant (Primary surfactant)
3. Co-surfactant (Secondary surfactant)
4. Co-Solvent

1. Oil phase

Oil segment Oil section is 2nd most vital automobile after water due to its houses to solubilise lipophilic drug molecules and improve absorption through lipid layer current in body.6 Oil has special property of penetrating phone wall and therefore very useful for lipophilic active drug delivery. Swelling of tail crew place of the surfactant is influence by means of oil phase. Such penetration is to greater extent in case of brief chain alkanes as in contrast to long chainalkanes.

Example Saturated fatty acids: lauric, myristic and capric acid Unsaturated fatty acids: oleic acid, linoleic acid and linolenic acid Fatty acid esters: ethyl or methyl esters of lauric, myristic and oleic acid Surfactants During the instruction of the microemulsion,surfactantmustbeableto reducetheinterfacialtensionnearest to zeroto facilitate dispersion of all components. These surfactants can be:
Non-ionic
Anionic
Cationic
Zwitterionic,

Nature of surfactants helps in determining steadiness of microemulsion.Dipole and hydrogen bond interactions stabilizes non-ionic surfactant and electrical double layer stabilizes ionic surfactants. Ionic surfactants are also affected by salt concentration. Hence ionic surfactants being sensitive in steadiness issues and due to toxicity concern, are generally nor preferable. But non-ionic surfactants can produce nontoxic pharmaceutical dosage forms and therefore greater popular.8 Surfactants with HLB values3-6 are beneficial in training of W/O micro emulsion and surfactants with higher HLB values8-18 are beneficial in instruction of O/W micro emulsion. Surfactants with more than 20 HLB values are acts as co-surfactant to minimize concentrations of surfactants to a applicable restriction and micro emulsion formation.

Examples of non-ionicsurfactants:
Polyoxyl 35 castor oil (Cremophor EL)
Polyoxyl forty hydrogenated castor oil (Cremophor RH 40)
Polysorbate20(Tween20)
Polysorbate80(Tween80)
d-α-tocopherolpolyethylene glycol1000succinate(TPGS)
SolutolHS-15 Sorbitanmonooleate(Span80)
Polyoxyl40 stearate,
PolyglycolyzedglycerideslikeLabrafilM-1944CS,LabrafilM-2125CS, Labrasol, Gellucire 44/14, etc.

Co-surfactants

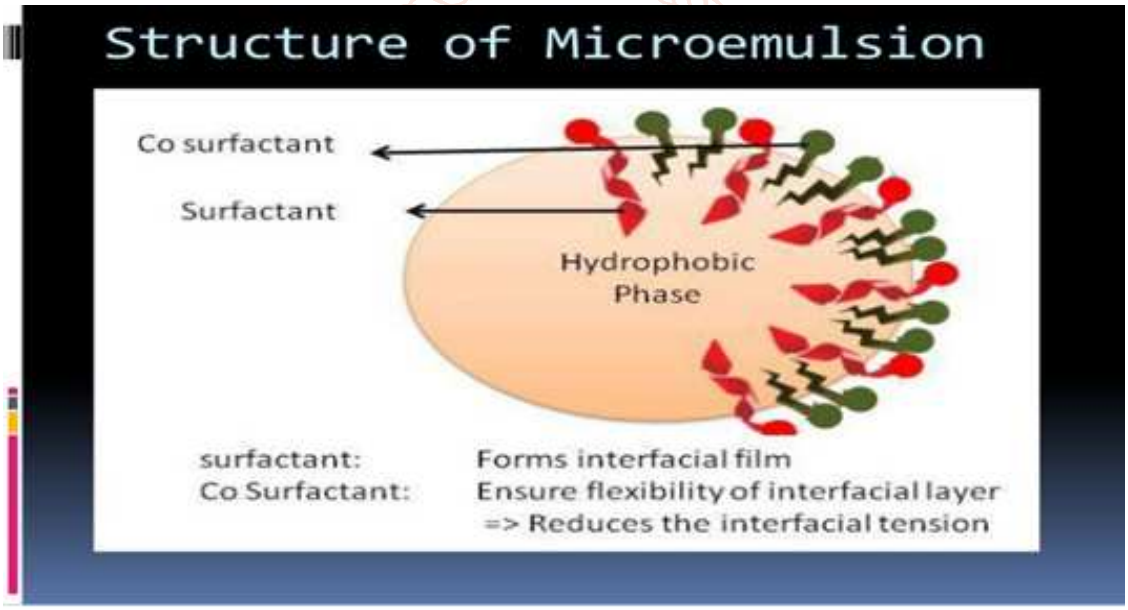
It is studied that excessive concentrations of single-chain surfactants are required to minimize the O/W interfacial anxiety to a level to enable a spontaneous formation of a microemulsion. However, if co-surfactants are delivered then with minimum attention of surfactants one of a kind curvatures of interfacial movie can be formed to generate steady micro emulsion composition. (11-16) Co surfactants raises the fluidity of the interface due to presence of fluidizing groups like unsaturated bonds, then demolishes liquid crystalline or gel shape and alters the HLB cost in such way to cause spontaneous formation of micro emulsion.
Example: Short chain alcohols like ethanol to butanol

Short chain glycols like propylene glycol
Medium chain alcohols like amines or acids
Types
Oil-in-water (o/w)
Water-in-oil (w/o)
Oil-in-water-in-oil (o/w/o)
Water-in-oil-in-water (w/o/w)

List of component used in microemulsion

Type of Excipient	Name of Excipient	Solubility(mg/ml)
	IPM	35.89
Oil	Ethyl oleate	5.89
	Oleic acid	3.98
	AOT	25.68
Surfactants	Span-20	8.65
	Tween-80	3.65
	PEG-400	2.65
	Butanol	3.62
Co-surfactant	Hexane	2.58
	Octanol	1.36
	Polaxomer 188	0.85
	Type I water	0.0008
Vehicles	Methanol	12.36
	Ethanol	15.23

Structure of microemulsion



For antifungal drug delivery:

It is usual that to elicit a pharmacologic response following topical administration, capsules need to enter and diffuse across the skin. The rate and extent of transport will rely on the interplay between the drug molecular homes and the traits of the biologic tissue. The drug may additionally additionally engage with specific proteins or other membrane components. These interactions can prolong residence time and therapeutic effect; for example, azoles have affinity for keratin just like dermatophytes which are their therapeutic target. Drug houses that amplify permeability across a given membrane may render the molecule much less fine at some other biologic tissue; the stratum corneum (SC) is a lipid barrier, in consequence, formulation design and optimization are key steps in increasing the therapeutic efficacy of topical antifungal therapy (25)

Preparation method of microemulsion(26-35)

Following are the method used for the preparation of the micro emulsion:

1. Phase titration method:
2. Phase inversion method:

1. Phase Titration Method

Micro emulsions are prepared by way of the spontaneous emulsification method (phase titration method) and can be depicted with the help of phase diagrams. Construction of segment format is a beneficial strategy to learn about the complicated collection of interactions that can take place when specific elements are mixed. Micro emulsions are shaped alongside with a number of affiliation buildings (including emulsion, micelles, lamellar, hexagonal, cubic, and a range of gels and oily dispersion) depending on the chemical composition and concentration of every component. The appreciation of their phase equilibrium

and demarcation of the segment boundaries are vital elements of the study. As quaternary phase graph (four aspect system) is time consuming and challenging to interpret, pseudo ternary section sketch is often developed to discover the specific zones together with micro emulsion zone, in which each corner of the plan represents 100% of the particular component. The region can be separated into w/o or o/w micro emulsion by sincerely thinking about the composition that is whether or not it is oil rich or water rich. Observations need to be made carefully so that the metastable structures are now not included.

2. Phase Inversion Method

Phase inversion of micro emulsions occurs as a result of addition of excess of the dispersed segment or in response to temperature. During section inversion drastic physical modifications appear which includes changes in particle measurement that can affect drug launch each in vivo and in vitro. These techniques make use of altering the spontaneous curvature of the surfactant. For non-ionic surfactants, this can be finished by using altering the temperature of the system, forcing a transition from an o/w micro emulsion at low temperatures to a w/o micro emulsion at higher temperatures (transitional section inversion). During cooling, the gadget crosses a factor of zero spontaneous curvature and minimal floor tension, merchandising the formation of finely dispersed oil droplets. This approach is referred to as phase inversion temperature (PIT) method. Instead of the temperature, different parameters such as salt concentration or pH price can also be considered as properly as an alternative of the temperature alone. Additionally, a transition in the spontaneous radius of curvature can be received via changing the water extent fraction. By successively including water into oil, at the beginning water droplets are fashioned in a non-stop oil phase. Increasing the water quantity fraction adjustments the spontaneous curvature of the surfactant from at first stabilizing a w/o micro emulsion to an o/w micro emulsion at the inversion locus. Short-chain surfactants structure flexible monolayer at the o/w interface resulting in a discontinuous micro emulsion at the inversion.

List of drug used in a preparation of microemulsion

Drug	Product name	Company	Therapeutic area
Cyclosporine	Sandimmune oral	Novartis	Immunosuppressant
Cyclosporine	Neoral	Novartis	Immunosuppressant
Calcitrol	Rocaltrol	Roche	Calcium regulator
Clofazimine	Lamprene	Geigy	Leprosy
Doxercalciferol	Hectoral	Bone care	Calcium regulator
Dronabionol	Marinol	Roxane	Anoxeria
Dutasteride	Avodart	GSK	Benign Prostatic Hyperplasia (BPH)
Isotretionoin	Accutane	Roche	Acne
Ritonavir	Norvir	Abbott	AIDS
Ritonavir/lopinavir	Kaletra	Abbott	AIDS
Paricalcitol	Zemplar	Abbott	Calcium regulator
Progesterone	Prometrium	Solvay	Endometrial hyperplasia
Saquinavir	Fortovase	Roche	AIDS
Sirolimus	Rapumune	Wyeth-ayerst	Immunosuppressant
Tritionoin	Vesanoid	Roche	Acne
Tipranavir	Aptivus	Boehringer Ingelheim	AIDS
Valproic acid	Depakene	Abbott	Epilepsy

Evaluation of microemulsion (28-36)

EVALUATION PARAMETERS OF MICROEMULSION SYSTEM

1. Physical appearance

For Physical look microemulsion can be investigate visually for homogeneity, fluidity and optical clarity.

2. Scattering Techniques(28)

Scattering strategies such as small angle neutron scattering, small perspective X-ray scattering and mild scattering have determined purposes in research of microemulsion structure, mainly in case of dilute monodisperese spheres, when polydisperse or concentrated systems such as those frequently considered in microemulsions.

3. Limpidity Test (Percent Transmittance) (29)

The limpidity of the microemulsion are often measured spectrophotometrically exploitation photometer

4. Drug stability (30)

The optimized microemulsion was unbroken beneath cold condition (4-8°C), temperature and at elevated temperature (50 ± two °C). once each two months the microemulsion will be analyzed for section separation, nothing transmission, orb size and a couple of assay.

5. Globule size and zeta potential measurements (31)

The orb size and letter potential of the microemulsion are often determined by dynamic lightweight scattering, employing a Zetasizer HSA 3000.

6. Assessment of the Rheological Properties (viscosity measurement) (32)

The physical science properties play a very important role in stability. It are often determined by Brookfield digital measuring system. modification within the physical science characteristics facilitate in deciding the microemulsion

region and its separation from alternative region. Bicontinuous microemulsion area unit dynamic structures with continuous fluctuations occurring between the bicontinuous structure, swollen reverse particle, and swollen micelles.

7. Electrical conductivity (33)

The water part was additional drop informed a combination of oil, chemical agent and co-surfactant and also the electrical conduction of developed samples is measured employing a conductometer at close temperature and at a continuing frequency of one cycle per second.

8. Drug solubility (34)

Drug was added in excess to the optimized microemulsion formulation similarly as every individual ingredient of the formulation. once continuous stirring for twenty-four h at temperature, samples were withdrawn and centrifuged at 6000 rate for ten min. quantity|the quantity|the number} of soluble drug within the optimized formulation similarly as every individual ingredient of the formulation was calculated by subtracting the drug gift within the sediment from the whole amount of drug added . The solubility of drug in microemulsion was compared with relation to its individual ingredients.

9. In-vitro drug release (35,36)

The diffusion study is allotted on a changed Franz diffusion cell, at intervals volume of 20mL. The receptor compartment was crammed with of buffer .The donor compartment was mounted with plastic wrap membrane, containing the microemulsion formulation and also the plain drug resolution, separately. At preset time intervals samples were withdrawn from the receptor compartment and analyzed for drug content, employing a ultraviolet light photometer at specific wavelength

Application of Microemulsion The application of micro-emulsion is given as follows ¬

- **Parenteral Delivery (37)**

Parenteral administration (especially via the intravenous route) of drugs with limited solubility is a major problem in industry because of the extremely low amount of drug actually delivered to a targeted site. Microemulsion formulations have distinct advantages over macroemulsion systems when delivered parenterally because of the fine particle microemulsion is cleared more slowly than the coarse particle emulsion and, therefore, have a longer residence time in the body.

- **Oral Delivery (38)**

Microemulsion formulations offer the several benefits over conventional oral formulation including increased absorption, improved clinical potency, and decreased drug toxicity. Therefore, microemulsions have been reported to be ideal delivery of drugs such as steroids, hormones, diuretic and antibiotics.

- **Topical delivery (39)**

Topical administration of drugs can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first-pass metabolism, salivary and degradation of the drug in stomach and related toxicity effects. Another is 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 (5flurouracil, apomorphine hydrochloride etc) and lipophilic drugs (estradiol, finasteride, ketoprofenetc) 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.

Other pharmaceutical applications (40,41,42,43,44)

- Nasal delivery
- Drug targeting
- Cellular targeting
- Brain targeting
- Periodontal delivery
- Tumor targeting

Conclusion

Microemulsion is drug delivery systems for the delivery of more than one medicament simultaneously. Microemulsion protect labile drug, control drug release, increase drug solubility, increase bioavailability and reduce patient variability also it has proven possible to formulate preparations suitable for most routes of administration. The role of microemulsion in providing novel solutions to overcome the problems of poor aqueous solubility of highly lipophilic drug compounds and provide high, more consistent and reproducible bioavailability. The drug delivery through the microemulsion is a promising area for the continued research with the aim of achieving the controlled release with enhanced bioavailability and for drug targeting to various sites of the body.

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