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MICROEMULSIONS: CURRENT TRENDS IN SUSTAINED RELEASE DRUG DELIVERY SYSTEMS

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Abstract
*Microemulsions are one of the best candidates as sustained drug delivery system because of their long shelf life, improved drug solubilization with ease of preparation and administration. A microemulsion is considered to be a thermodynamically or kinetically stable liquid dispersion of oil and a water phases, 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. These are 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 surfactant, the oil phase and the water phase. The main objective of this review paper is to discuss microemulsions asdrug carrier system with other pos*sible applications.

Keywords: Microemulsions, thermodynamically stable, amphiphilic, solubilization

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Introduction

SUSTAINED RELEASE: With many drugs the basic goal of therapy is to achieve a steady-state blood or tissue level that is therapeutically effective and nontoxic for an extended period of time. The design of proper dose regimens is an important element in accomplishing this goal. A basic objective in dosage form design is to optimize the delivery of medication so as to achieve a measure of control of the therapeutic effect in the face of uncertain fluctuation in the in vivo environment in which drug release takes place. This is usually accomplished by maximum drug availability i.e. by attempting to attain a maximum rate and extent of drug absorption however,control of drug action through formulation also implies controlling bioavailability to reduce drug absorption rate.[1]Sustained release system, only prolong therapeutic blood or tissue levels of the drug for an extended period time.[2]

Sustained release preparations are intended to reduce the frequency of the administration unlike multiple dose regimens. At the same time, it provides constant plasma drug level for longer time and, therefore, the drug effect is prolonged. Sustained release dosage form minimizes the fluctuations in the plasma drug level. Ideally sustained release preparation contains two fractions-one fraction releases the drug immediately to achieve the desired plasma level; the second fraction (maintenance dose) release the drug slowly to maintain the desired level for further period. Sustained release formulation is suitable only when the drug absorption taken place throughout the GI tract i.e.theophylline &propranolol.[3]

Advantages of sustained release drug delivery

1. Following are the potential advantages of sustained release products:
2. Decreased local and systemic side effects reduced gastrointestinal irritation.
3. Better drug utilization reduction in total amount of drug used.
4. Improved efficiency in treatment, optimized therapy, more uniform blood concentration
5. Reduction in fluctuation in drug level and hence more uniform pharmacological response, cure of control of condition more promptly, less reduction in drug activity with chronic use.
6. Economy, although the initial unit cost of sustained release products is usually greater than of the conventional dosage form because of the special nature of these products, the average cost of treatment over an extended time period may be less.

Disadvantages of sustained release drug delivery

The disadvantages of sustained release drug delivery system are-

A. Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time complete release, site specific absorption, pH dependent stability, etc.

B. Poor in vitro –in vivo correlation.

C. Possible reduction in systemic availability.

D. Need for additional patient education.

E. Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.

F. Reduced potential for dose adjustment of drugs normally administered in varying strengths.[4]

MICROEMULSION:-

Microemulsions are defined as clear, transparent, thermodynamically stable, isotropic mixtures of oil and water, frequently in combination with a co-surfactant. Recently microemulsion formulations are widely used for the delivery of hydrophilic as well as lipophilic drug as drug carriers due to their improved drug solubilization capacity, long shelf life, ease of preparation and improvement of bioavailability.[5]

A microemulsion is considered to be a thermodynamically or kinetically stable liquid dispersion of oil and a water phases, 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. These are 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 surfactant, the oil phase and the water phase.[6]

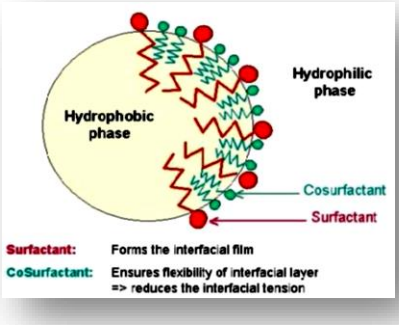

Fig.1-Structure of the combination of cosurfactant &surfactant in Microemulsion

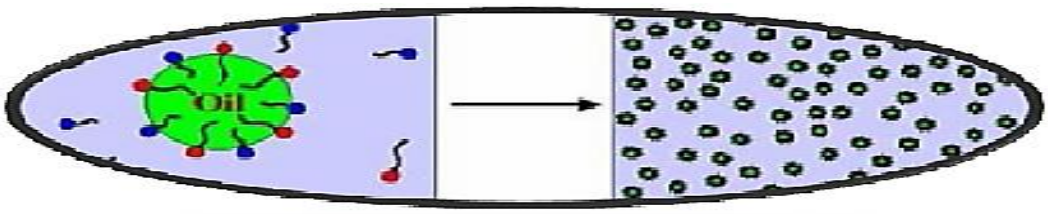

Fig. 2- Structure of Microemulsion

Table 1.1- Difference between Emulsion and Microemulsion:

Property	Emulsion (Macroemulsion)	Microemulsion
Appearance	Cloudy	Transparent
Optical isotropy	Anisotropic	Isotropic
Interfacial tension	High	Ultra-low
Microstructure	Static	Dynamic
Droplet Size	>500nm	20-200nm
Stability	Thermodynamically unstable	Thermodynamically stable and long shelf life
Phases	Biphasic	Monophasic
Preparation	Require a large input of energy	Facile preparation
Viscosity	High Viscosity	Low viscosity with Newtonian behavior
Turbidity	Turbid	Transparent
Co-surfactant used	No	Yes
Surfactant concentration	0.5-5µ	<0.1µ
Molecular packing	Inefficient	Efficient

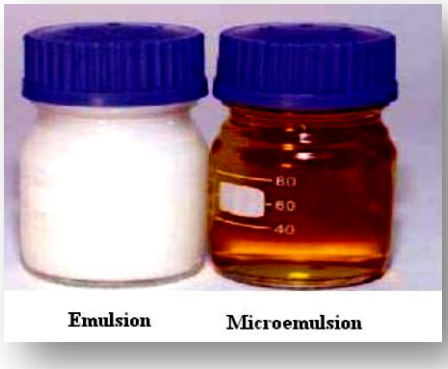

Fig. 3-Comparisons between Emulsion and Microemulsion

TYPES OF MICROEMULSIONS:

Microemulsions are thermodynamically stable,but are only found under carefully definedconditions.[5-7]According to Winsor, fourtypes of microemulsion phases exist in equilibria;which are also referred as Winsor phases.They are as follows-

A. Oil- in- water microemulsion or winsor I:-

It consists of O/W microemulsions in equilibrium with excess oil phase. The surfactant is preferentially soluble in water and oil in- water (O/W) microemulsions form (Winsor I). The surfactant rich water phase coexists with the oil phase where surfactant is only present as monomers at small concentration.

B. Water - in - oil microemulsion or winsor II:-

It consists of W/O microemulsions in equilibrium with excess water phase. The surfactant is mainly in the oil phase and water in- oil (W/O) microemulsions form.The surfactant-rich oil phase coexists with the surfactant-poor aqueous phase (Winsor II).

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C. Bicontinuous microemulsion or winsor III :-

It consists of microemulsion phase in equilibrium with both excess water and excess oil phase. A three-phase system where a surfactant-rich middle-phase coexists with both excess water and oil surfactant-poor phases (Winsor III or middle-phase microemulsion).

D. Single phase homogeneous mixture or winsor IV:-

A single-phase (isotropic) micellar solution, that forms upon addition of a sufficient quantity of amphiphile (surfactant plus alcohol).

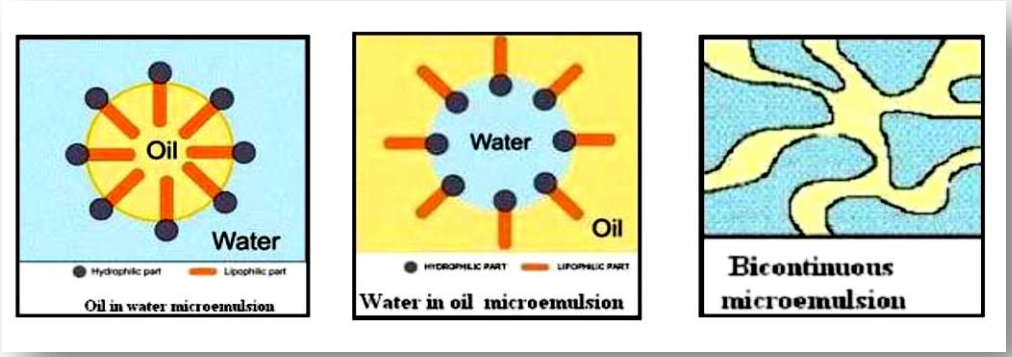

Fig. 4- Types of Microemulsions

Advantages of microemulsion based system:-[5,7,11]

A. Microemulsions can solubilize hydrophilic and lipophilic drugs including drugs that are relatively insoluble in both aqueous and hydrophobic solvents. This is due to existence of microdomains of different polarity within the same single phase solution.

B. Microemulsions are thermodynamically stable system and the stability allows self-emulsification of the system whose properties are not dependent on the process followed.

C. Microemulsion based system has long shelf life.

D. The use of microemulsion as delivery system can improve the efficacy of a drug, allowing the total dose to be reduced and thus minimizing side effects.

E. The formation of microemulsion is reversible. They may become unstable at low or high temperature but when the temperature returns to the stability range, the microemulsion reforms.

F. Good penetration of hydrophilic, low molecular weight drugs can be obtained through the eye.Avoidance of hepatic first pass metabolism and thus potential for dose reduction compared to oral delivery.

G. The use of microemulsion as delivery systems can improve the efficacy of a drug allowing the total dose to be reduced and thus minimizing side effects.

H. The formation of microemulsion is reversible. They may become unstable at low or high temperature but when the temperature returns to the stability range, the microemulsion reforms.

METHOD OF PREPARATION OF MICROEMULSION:[6,8]

Microemulsions are prepared when interfacial tension at the oil/water is kept at very low level. Interfacial layer is kept very much flexible and fluid concentration of surfactants should be high enough to give surfactant molecules to be stabilized the microemulsion at an extremely low interfacial tension.

Two main methods are reported for the formulation of microemulsion, these are:

A. Phase Titration Method

B. Phase Inversion Method

Phase Titration Method:-

Microemulsions are prepared by spontaneous emulsification methodwhich is illustrated with help of phase diagrams. Phase diagram construction is practical approach to study complex series of interaction which occurs when different components are mixed. The aspect of the phase diagram is phase equilibrium and

demarcation of phase boundaries. Most often pseudo-ternary phase diagrams are constructed to figure out microemulsion zone as quaternary phase diagram is time consuming and difficult to interpret.

Phase Inversion Method:-

Phase inversion of microemulsion happens upon addition of excess of dispersed phase. Phase inversion leads to radical physical changes as change in particle size that alters drug release. During cooling, this system crosses the point of zero spontaneous curvature and minimal surface tension, prompting the formation of finely dispersed oil droplets. Microemulsions can be prepared by controlled addition of lower alkanols (butanol, pentanol and hexanol) to milky emulsions to produce transparent solutions comprising dispersions of either o/w or w/o or colloidal dispersions. The lower alkanols are called co-surfactants. They lower the interfacial tension between oil and water sufficiently low for almost spontaneous formation.

INGREDIENTS OF MICROEMULSION:-

Various ingredients are used in the formulation and development of microemulsions. Mainly oil and surfactants are used which must be biocompatible, non-toxic and clinically acceptable. Main components of microemulsion are as follows:

Oil phase:-Oil is one of the most important components of microemulsion because it can solubilize the required dose of the lipophilic drug and it increases the fraction of lipophilic drug transported via the intestinal lymphatic system. Oil is defined as any liquid having low polarity and low miscibility with water. The examples of such phase are cyclohexane, mineral oil, toluene, & vegetable oil etc.

Aqueous phase:-Generally the aqueous phase contains hydrophilicactive ingredients and preservatives. Sometimesbuffer solutions are used as aqueous phase.

Surfactant:- The term surfactant (surface-active-agent) denotes a substance which exhibits some superficial or interfacial activity & used to lower the surface or interface tension. It has affinity for polar & nonpolar solvents. Surfactants are the molecules that contain a polar head group and a nor-polar tail. Surfactant molecules self-associate due to various inter- and intra-molecular forces as well as entropy considerations. The various types of surfactants that help in the progressive development of microemulsion system are as follows.

Types of surfactant:

1. **Primary surfactant-**The surfactant are generally ionic, non-ionic or amphoteric. The surfactant chosen are generally from the non-ionic group because of their good cutaneous tolerance. Only for specific case amphoters are being investigated.Commonly used surfactant are as follows-

A. Anionic surfactant: They can penetrate and interact strongly with skin. Examples- Dioctyl sulphosuccinate, Sodium lauryl sulphate, Decodecylmethyl sulphoxide etc.

B. Cationic surfactant: Cationic surfactants are reportedly more irritating than anionic surfactants and they have not been widely studied as skin permeation enhancer.

C. Nonionic surfactant: Nonionic surfactants have least potential for irritation. Example- Pluronic F127, Pluronic F68 etc.

D. Miscellaneous chemicals: These includes urea, N,N-dimethyl-m-toluamide, calcium thioglycolate etc.

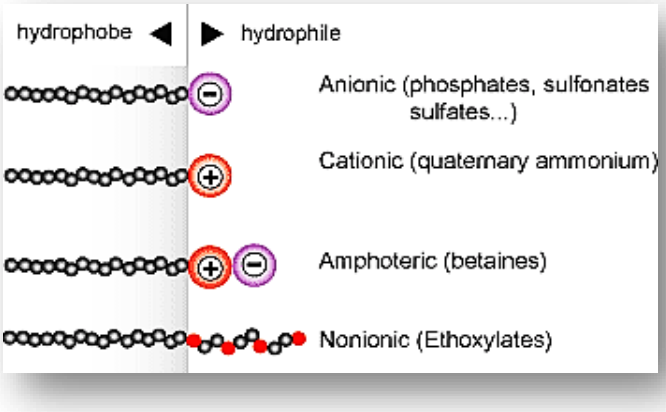

Fig. 5- Types of surfactant

2. Secondary surfactant:
It is otherwise called as co-surfactant. The co-surfactant originally used are of short chain fatty alcohol i.e. pent&hexanoland benzyl alcohol. These are most often polyols, esters of polyols derivatives of glycerol & organic acids, Poloxamer, Polysorbate 80 and Span 20,Cinnamic alcohol, Cinnamicaldehyde etc.Their main purpose is to make the interfacial film fluid by themselves between the surfactant molecules. [6]

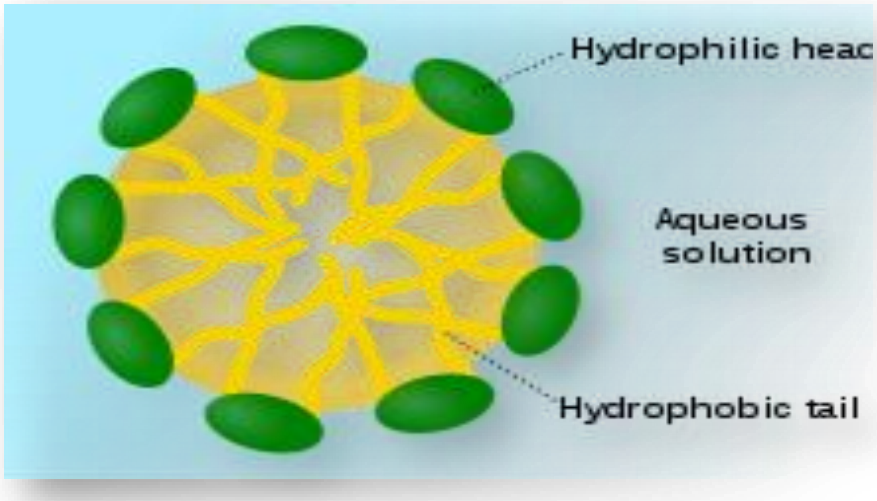

Fig. 6- Structure of surfactant

Co-solvent :- It has been observed that single-chain surfactants are unable to reduce the o/w interfacial tension sufficiently to form a microemulsion. The addition of co-surfactants allows the interfacial film to be flexible to take up different curvatures required to form microemulsion over a wide range of excipients. If a single surfactant film is desired, the lipophilic chains of the surfactant should be sufficiently short, or contain fluidizing groups (e.g. unsaturated bonds). Basic co-surfactants are short chain alcohols (ethanol to butanol), glycols such as propylene glycol, medium chain alcohols, amines or acids. The use of co-surfactant is to destroy liquid crystalline or gel structures that come in place of a microemulsion phase.

Factors to Be Considered During Preparation of Microemulsion:
Three important conditions:
A. Surfactants must be chosen carefully so that an ultra-low interfacial tension (< 10 mN/m) can be attained at the oil / water interface which is a prime requirement to produce microemulsions.

B. Concentration of surfactant must be high enough to provide the number of surfactant molecules needed to stabilize the micro droplets to be produced by an ultra-low interfacial tension.
C. The interface must be flexible or fluid enough to promote the formation of microemulsions.[12-14]

APPLICATION OF MICROEMULSION SYSTEM:-

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

A. Parenteral Delivery:-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.

B. Oral Delivery:- 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.

C. Topical delivery:-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 (5- flurouracil, 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.

D. Ophthalmic delivery:- In conventional ophthalmic dosage forms, water soluble drugs are delivered in aqueous solution while water insoluble drugs are formulated as suspension or ointments. 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.

E. Nasal delivery:-Recently, microemulsions are being studied as a delivery system to enhance uptake of drug through nasal mucosa. In addition with mucoadhesive polymer helps in prolonging residence time on the mucosa.

F. Other pharmaceutical applications:-

a) Drug targeting
b) Cellular targeting
c) Brain targeting
d) Periodontal delivery[15]

CONCLUSION:-Microemulsions have a very crucial importance in the drug delivery system as well as in the industrial process. They can be used to optimize drug targeting without a concomitant increase in systemic absorption. The role of microemulsion is to provide novel solutions to overcome the problems of poor aqueous solubility of highly lipophilic drug compounds and provide high, more consistent and reproducible bioavailability. Microemulsion thus prepared would improve the bioavailability due to their improved drug solubilization capacity, long shelf life and ease of preparation. Simultaneously, the dosing frequency would be reduced due to sustained action of microemulsion formulation. In addition to this, the patient compliance would also improve. In today's world Microemulsion is accepted as full of potential for novel drug delivery systems. Current research work is focused on the preparation of safe, efficient and more compatible microemulsion constituents which will further enhance the utility of these novel vehicles.

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