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NSAID Microemulsion In Treatment of Rheumatoid Arthritis

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ABSTRACT

Rheumatoid arthritis is a common inflammatory disease characterized by progressive bone and cartilage destruction, A full cure for rheumatoid arthritis is yet to be discovered but Microemulsion containing NSAID can be used as best option for the management of pain in Rheumatoid arthritis because of their potential to incorporate a wide range of drug molecules (hydrophilic and hydrophobic) due to the presence of both lipophilic and hydrophilic domains.

Association of drugs with Microemulsion is normally noncovalent, based on collective strength of weak binding forces which are broken to release drug. The small droplets of Microemolsion provide better adherence to membranes and transport NSAID molecules in a controlled fashion for the pain management of Rheumatoid Arthritis. These adaptable delivery systems provide protection against oxidation, enzymatic hydrolysis and improve the solubilization of lipophilic drugs and hence enhance their bioavailability.

Keywords: Rheumatoid arthritis, Microemulsion, NSAID, Lipophilic domain, Hydrophilic domains.

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INTRODUCTION

Microemulsions are modern colloidal drug carrier systems. A microemulsion made from water, oil, surfactants and co-surfactant is a thermodynamically stable system. The presence of the co-surfactant is often required in order to decrease the interfacial tension between aqueous and non-aqueous phase, because the fact that a low interfacial tension is essential in microemulsions formation. Microemulsions represent a potential and powerful alternative carrier system for transdermal drug delivery because of their high solubilization capacity, transparency, thermodynamic stability, facility of preparation, and high diffusion and absorption rates.

Rheumatoid arthritis- an auto immune disease:-

Rheumatoid Arthritis appears to be an autoimmune disease driven primarily by activated T cells, giving rise to T cell-derived cytokines, such as IL-1 and TNF-a. Activation of B cells and the humoral response also are evident, although most of the antibodies generated are IgGs of unknown specificity, apparently elicited by polyclonal activation of B cells rather than from a response to a specific antigen. Rheumatoid arthritis is a chronic disease in which various joints in the body are inflamed, leading to swelling, pain, stiffness, and the possible loss of function[1].

Many cytokines, including IL-1 and TNF-a, have been found in the rheumatoid synovium. Glucocorticoids interfere with the synthesis and actions of cytokines, such as IL-1 or TNF-a. Although some of the actions of these cytokines are accompanied by the release of prostaglandins and thromboxane A_2 (TXA_2), COX inhibitors appear to block only their pyrogenic effects. In addition, many of the actions of the prostaglandins are inhibitory to the immune response, including suppression of the function of helper T cells and B cells and inhibition of the production of IL-1 .Thus, it has been suggested that COX-independent effects may contribute to the efficacy of NSAIDs in this setting[2].

NSAID in rheumatoid artharitis[3]:-

Although non steroidal anti-inflammatory drugs are still widely used to lessen pain, they are no longer considered first-line treatment because of their limited effectiveness, inability to modify disease course in the long term. Few NSAIDs efficiently interferes with Neutrophils adhesion to endothelium and this effect may represent an additional relevant mechanism in its anti-inflammatory activity. Few NSAID has an outstanding anti-inflammatory profile, involving a classical inhibition of prostaglandins E_2, a decrease in the expression of several cytokines including interleukin and tumor necrosis factor. It also inhibits activated oxygen species production and influences cell adhesion. Thus it can be concluded that NSAID may be a better

option for the management of pain. Aceclofenac ([[[2-[(2,6-Dichlorophenyl)amino]phenyl]acetyl]oxy]acetic acid.) is superior form other NSAIDs as it has selectivity for cox-2, a beneficial cox inhibitor, well tolerated, better GI tolerability and improved cardiovascular safety when compared to other selective cox-2 inhibitors. It also shows Increased matrix component synthesis and protection of chondrocytes against apoptosis.

Microemulsion for topical drug delivery:-

In 1959, Schulman *et al*. visualized the existence of small emulsion-like structures by electron microscopy and subsequently coined the term "microemulsions". The microemulsion concept was introduced as early as the 1940s by Hoar and Schulman who generated a clear single-phase solution by titrating a milky emulsion with hexanol .Schulman and coworkers (1959) subsequently coined the term definite and it has since been defined and indeed redefined on many occasions. Danielsson and Lindman in 1981 defined microemulsion as 'a system of water, oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution[4].

These versatile systems are currently of great technological and scientific interest to the researchers because of their potential to incorporate a wide range of drug molecules (hydrophilic and hydrophobic) due to the presence of both lipophilic and hydrophilic domains. These adaptable delivery systems provide protection against oxidation, enzymatic hydrolysis and improve the solubilisation of lipophilic drugs and hence enhance their bioavailability. In addition to oral and intravenous delivery, they are amenable for sustained and targeted delivery through ophthalmic, dental, pulmonary, vaginal and topical routes. Microemulsions are experiencing a very active development as reflected by the numerous publications and patents being granted on these systems. Microemulsions as drug delivery tool show favourable properties like thermodynamic stability (long shelf-life),easy formation (zero interfacial tension and almost spontaneous formation), optical isotropy, ability to be sterilized by filtration, high surface area (high solubilization capacity) and very small droplet size. The small droplets also provide better adherence to membranes and transport drug molecules in a controlled fashion. Microemulsions are easy to administer to children and to people who have difficulty swallowing solid oral dosage forms. The drug delivery system should be mild and biocompatible, the choice of excipients is, however, limited. Also a large amount of surfactant is required for microemulsion formation which is undesirable. Therefore, proper selection of the components and their use concentration is imperative for a wider acceptability. The field of existence of microemulsion is

generally narrow and their temperature stability, particularly of non-ionic surfactant containing microemulsions, can be limited[5].

Absorption through skin:[6-8]

Two principal absorption routes are identified:

Transepidermal absorption

It is now generally believed that the transepidermal pathway is principally responsible for diffusion across the skin. The resistance encountered along this pathway arises in the stratum corneum. Permeation by the transepidermal route first involves partitioning into the stratum corneum. Diffusion then takes place across this tissue. The current popular belief is that most substances diffuse across the stratum corneum via the intercellular lipoidal route. This is a tortuous pathway of limited fractional volume and even more limited productive fractional area in the plane of diffusion. However, there appears to be another microscopic path through the stratum corneum for extremely polar compounds and ions. Otherwise, these would not permeate at rates that are measurable considering their o/w distributing tendencies. When a permeating drug exits at the stratum corneum, it enters the wet cell mass of the epidermis and since the epidermis has no direct blood supply, the drug is forced to diffuse across it to reach the vasculature immediately beneath. The viable epidermis is considered as a single field of diffusion in models. The epidermal cell membranes are tightly joined and there is little to no intercellular space for ions and polar nonelectrolyte molecules to diffusionally squeeze through. Thus, permeation requires frequent crossings of cell membranes, each crossing being a thermodynamically prohibitive event for such water-soluble species. Extremely lipophilic molecules on the other hand, are thermodynamically constrained from dissolving in the watery regime of the cell (cytoplasm). Thus the viable tissue is rate determining when nonpolar compounds are involved.

Passage through the dermal region represents a final hurdle to systemic entry. This is so regardless of whether permeation is transepidermal or by a shunt route. Permeation through the dermis is through the interlocking channels of the ground substance. Diffusion through the dermis is facile and without molecular selectivity since gaps between the collagen fibers are far too wide to filter large molecules. Since the viable epidermis and dermis lack measure physiochemical distinction, they are generally considered as a single field of diffusion, except when penetrants of extreme polarity are involved, as the epidermis offers measurable resistance to such species.

Transfollicular (shunt pathway) absorption

The skin's appendages offer only secondary avenues for permeation. Sebaceous and eccrine glands are the only appendages, which are seriously considered as shunts bypassing the stratum corneam since these are distributed over the entire body. Though eccrine glands are numerous, their orifices are tiny and add up to a miniscule fraction of the body's surface. Moreover, they are either evacuated or so profusely active that molecules cannot diffuse inwardly against the glands output. For these reasons, they are not considered as a serious route for percutaneous absorption. However, the follicular route remains an important avenue for percutaneous absorption since the opening of the follicular pore, where the hair shaft exits the skin, is relatively large and sebum aids in diffusion of penetrants. Partitioning into sebum, followed by diffusion through the sebum to the depths of the epidermis is the envisioned mechanism of permeation by this route. Vasculature sub serving the hair follicle located in the dermis is the likely point of systemic entry. Absorption across a membrane, the current or flux is and terms of matter or molecules rather than electrons, and the driving force is a concentration gradient (technically, a chemical potential gradient) rather than a voltage drop. A membranes act as a "diffusional resistor." Resistance is proportional to thickness (h), inversely proportional to the diffusive mobility of matter within the membrane or to the diffusion coefficient (D), inversely proportional to the fractional area of a route where there is more than one (F), and inversely proportional to the carrying capacity of a phase.

$$\mathbf{R = h/FDK}$$

R =Resistance of diffusion resistor; H = Thickness, F = Fractional area ; D = diffusivity ; K = Relative capacity

Basic principle of permeation: [9]

In the initial transient diffusion stage, drugs molecules may penetrate the skin along the hair follicles or sweat ducts and then be absorbed through the follicular epithelium and sebaceous glands. When a steady state has been reached diffusion through stratum corneam becomes the dominant pathway.

The membrane-limited flux (J) under steady condition is described by expression.

$$J = \frac{DAK_{O/W}\, r\, C}{h}$$

Where:

J = Amount of drug passing through the membrane system per unit area, per unit area per unit time.

D= Diffusion coefficient

A= Area of the membrane

C= Concentration gradient

$K_{o/w}$= Membranes / vehicle partition coefficient

h= Thickness of the membrane.

Kinetics of permeation: [6-8]

Knowledge of skin permeation is vital to the successful development of topical formulation. Permeation of a drug involves the following steps,

- Sorption by stratum corneum,
- Penetration of drug though viable epidermis,
- Uptake of the drug by the capillary network in the dermal papillary layer.

This permeation can be possible only if the drug possesses certain physicochemical properties. The rate of permeation across the skin (dQ/dt) is given by:

$$\frac{dQ}{dt} = P_s(c_d - c_r)$$

Where C_d and C_r are, the concentrations of skin penetrants in the donor compartment (e. g., on the surface of stratum corneum) and in the receptor compartment (e.g., body) respectively. P_s is the overall permeability coefficient of the skin tissues to the penetrant. This permeability coefficient is given by the relationship:

$$P_s = \frac{K_s D_{ss}}{H_s}$$

Where K_s is the partition coefficient for the interfacial Partitioning of the penetrant molecule form a solution medium on to the stratum corneum, D_{ss} is the apparent diffusivity for the steady state diffusion of the penetrants molecule through a thickness of skin tissues and $h_s$is the overall thickness of skin tissues. As K_s, D_{ss} and hs are constant under given conditions, the permeability coefficient (P_s) for a skin penetrant can be considered to be constant.

From equation (1) it is clear that a constant rate of drug permeation can be obtain when $C_d >> C_r$ i.e., the drug concentration at the surface of the stratum corneum(C_d) is consistently and substantially greater than the drug concentration in the body (C_r). The equation (1) becomes: and the rate of skin permeation (dQ/dt) is constant provide the magnitude of C_d remains fairly constant throughout the course of skin permeation. For keeping C_d constant, the drug should be

released from the device at a rate (R_r) that is either constant or greater than the rate of skin uptake (R_a) i.e., $R_r >> R_a$.

Factor affecting topical permeation:

Physicochemical properties of drug substances[10-11]

A. Partition coefficient
B. pH-condition
C. Drug solubility
D. Concentration
E. Particle size
F. Polymorphism
G. Molecular weight

Penetration enhancer [12-17]

Percutaneous absorption can be enhancing in two ways either by chemical enhancer or by physical method.

Chemical penetration enhancer:

By definition, a chemical skin penetration enhancer increase skin permeability by reversibly damaging or by altering the physicochemical nature of the stratum corneum to reduce its diffusional resistance. Among the alterations are increased hydration of stratum corneum and / or a change in the structure of the lipids and lipoproteins in the intercellular channels through solvent action or denaturation. These may conveniently be classified under the following main heading:

Solvents:

These compounds increase penetration possibly by swelling the polar pathway and/or by fluidizing lipids. Examples include water, alcohols, methanol and ethanol; alkyl methyl sulfoxide, dimethyl sulfoxide, alkyl homologs of methyl sulfoxide, dimethyl acetamide and dimethylformamide; pyrrolidones- 2 -pyrrolidone, N-methyl, 2- pyrrolidone; laurocapram (Azone), miseellancous solvents- propnylene glycol, glyeerol, silicone fluids, isopropyl palmitate.

Surfactant:

These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. The ability of the surfactant to alter penetration is a function of polar head group and the hydrocarbon chain length. Commonly used surfactant are as follow

Anionic surfactant: can penetrants and interact strongly with skin. Examples include are Dioctylsulphosuccinate, Sodium lauryl sulphate, Decodecylmethylsulphoxide etc.

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

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

Bile salts: Sodium taurocholate, Sodium deoxycholate, and Sodium tauroglycocholate.

Binary system: These systems apparently open the heterogeneous multi laminated pathway as well as the continuous pathways. Examples include are Prolylene glycol -oleic acid and 1,4-butane diol- linoleic acid.

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

Advantages of microemulsion based system:[18]

Microemulsion exhibits several advantages as a drug delivery system:

1. Microemulsions are thermodynamically stable system and the stability allows self emulsification of the system whose properties are not dependent on the process followed.
2. Microemulsions can be described as super solvents of the drug. They can solubilized hydrophilic and lipophilic drugs including drugs that are relatively insoluble in both aqueous and hydrophobic solvents. This is due to existence of micro domain of different polarity within the same single-phase solution.
3. .The dispersed phase, lipophilic or hydrophilic (oil-in-water, O/W, or water-in-oil, W/o microemulsions)can behave as a potential reservoir of lipophilic or hydrophilic drugs, respectively. The drug partitions between dispersed and continuous phase, and when the system come into contact with semi-permeable membrane, the drug can be transported through the barrier. 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 mean diameter of droplets in microemulsions is below 0.22nm, they can be sterilized by filtration. The small size of droplets in microemulsions e.g. below 100nm, yields very large interfacial area, from which the drug can quickly be released into external phase when absorption (in vitro or in vivo) takes place, maintaining the concentration in the external phase close to initial levels.
5. Same microemulsions can carry both lipophilic and hydrophilic drugs.

6. Because of thermodynamic stability, microemulsion are easy to prepare and require no significant energy contribution during preparation. Microemulsion have low viscosity compared to other emulsion.
7. The use of microemulsion as delivery systems can improve the efficiency of a drug, allowing the total dose to be reduced thus minimizing the side effects.
8. 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.

Disadvantages of microemulsion based systems:[19]

1. Use of a large concentration of surfactant and co-surfactant necessary for stabilizing the nanodroplets.
2. Limited solubilizing capacity for high-melting substances
3. The surfactant must be non-toxic for using pharmaceutical applications.
4. Microemulsion stability is influenced by environmental parameters such as temperature and pH. These parameters change upon microemulsion delivery to patients.

Structure:[18]

Microemulsions are dynamic systems in which the interface is continuously and spontaneously fluctuating. Structurally, they are divided into oil-in-water (o/w), water in-oil (w/o) and bicontinuous microemulsions. In w/o microemulsion, water droplets are dispersed in the continuous oil phase while o/w microemulsion is formed when oil droplets are dispersed in the continuous aqueous phase. In systems where the amounts of water and oil are similar, a bicontinuous microemulsion may result. In all three types of microemulsions, the interface is stabilized by an appropriate combination of surfactants and/or co-surfactants. The mixture of oil, water and surfactants is able to form a wide variety of structures and phases depending upon the proportions of the components. The flexibility of the surfactant film is an important factor in this regard. A flexible surfactant film will enable the existence of several different structures like droplet like shapes, aggregates and bi continuous structures, and therefore broaden the range of micro emulsion existence. A very rigid surfactant film will not enable existence of discontinuous structures, which will impede the range of existence. Besides micro emulsions, structural examinations can reveal the existence of regular emulsions, anisotropic crystalline hexagonal or cubic phases, and lamellar structures depending on the ratio of the components.

Theories of microemulsion formation:[20]

Historically, three approaches have been used to explain microemulsion formation and stability

They are as follows-

Interfacial or mixed film theories.

Solubilization theories.

Thermodynamic treatments.

The free energy of microemulsion formation can be considered to depend on the extent to which surfactant lowers the surface tension of the oil water interface and change in entropy of the system such that,

$$Gf = \gamma a - T S$$

Where, **Gf** = free energy of formation

A = change in interfacial area of microemulsion

S = change in entropy of the system

T = temperature

γ = surface tension of oil water inter phase

It should be noted that when a microemulsion is formed the change in A is very large due to the large number of very small droplets formed. In order for a microemulsion to be formed (transient) negative value of was required, it is recognized that while value of is positive at all times, it is very small and it is offset by the entropic component. The dominant favorable entropic contribution is very large dispersion entropy arising from the mixing of one phase in the other in the form of large number of small droplets. However there are also expected to be favourable entropic contributions arising from other dynamic processes such as surfactant diffusion in the interfacial layer and monomer-micelle surfactant exchange. Thus a negative free energy of formation is achieved when large reductions in surface tension are accompanied by significant favourable entropic change. In such cases, microemulsion is spontaneous and the resulting dispersion is thermodynamically stable.

Types of microemulsion systems:[20]

According to Winsor, there are four types of microemulsion phases exists in equilibria, these phases are referred as Winsor phases. They are,

1. winsor i: With two phases, the lower (o/w) microemulsion phases in equilibrium with the upper excess oil.

2. winsor ii: With two phases, the upper microemulsion phase (w/o) microemulsion phases in equilibrium with lower excess water.

3. winsor iii: With three phases, middle microemulsion phase (o/w plus w/o, called bicontinous) in equilibrium with upper excess oil and lower excess water.

4.winsor iv: In single phase, with oil, water and surfactant homogenously mixed.

Ternary phase diagram:-[21]

The microemulsion region is usually characterized by constructing ternary-phase diagrams. Three components are the basic requirement to form a microemulsion: an oil phase, an aqueous phase and a surfactant. If a co surfactant is used, it may sometimes be represented at a fixed ratio to surfactant as a single component, and treated as a single

"pseudo-component". The relative amounts of these three components can be represented in a ternary phase diagram. 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. The three components composing the system are each found at an apex of the triangle, where their corresponding volume fraction is 100%. Moving away from that corner reduces the volume fraction of that specific component and increases the volume fraction of one or both of the two other components. Each point within the triangle represents a possible composition of a mixture of the three components or pseudo-components, which may consist (ideally, according to the Gibbs' phase rule) of one, two or three phases. These points combine to form regions with boundaries between them, which represent the "phase behavior" of the system at constant temperature and pressure.

The Gibbs phase diagram, however, is an empirical visual observation of the state of the system and may, or may not express the true number of phases within a given composition. Apparently clear single phase formulations can still consist of multiple iso-tropic phases (e.g. the apparently clear heptane/AOT/water microemulsions consist multiple phases). Since these systems can be in equilibrium with other phases, many systems, especially those with high volume fractions of both the two immiscible phases, can be easily destabilized by anything that changes this equilibrium e.g. high or low temperature or addition of surface tension modifying agents. However, examples of relatively stable microemulsions can be found. It is believed that the mechanism for removing acid build up in car engine oils involves low water phase volume, water-in-oil (w/o) microemulsions. Theoretically, transport of the aqueous acid droplets through the engine oil to micro dispersed calcium carbonate particles in the oil should be most efficient when the droplets are small enough to transport a single hydrogen ion (the smaller the droplets, the greater the number of droplets, the faster the neutralization). Such microemulsions are probably very stable across a reasonably wide range of elevated temperatures.

Preparation of microemulsion:

Following are the methods of preparation used for the preparation of microemulsion:

Phase titration method

Phase inversion method

Phase titration method:

Microemulsion are prepared by the spontaneous emulsification method (phase titration method) and can be portrayed with the help of phase diagram. As quaternary phase diagram As quaternary phase diagram (four component system) is time consuming and difficult to interpret, pseudo ternary phase diagram is constructed to find out the different zones including microemulsion zone, in which each corner of the diagram represents 100% of the particular components. 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 mono phasic/ 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 mono phasic, 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 micro emulsion region of existence[20].

Fig 02: A hypothetical pseudo-ternary phase diagram of an oil/surfactant/water system with emphasis on microemulsion and emulsion phases. Within the phase diagram, existence fields are shown where conventional micelles, reverse micelles or water-in-oil(w/o) microemulsion and oil-in-water microemulsion are formed along with the bicontinuous microemulsion. At very high surfactant concentration two phase system are observed[19]

Phase inversion method

Phase inversion of microemulsion is carried out upon addition of excess of the dispersed phase or in response to temperature. During phase inversion drastic physical changes occur including changes in particle size that can ultimately affect drug release both in vitro and in vivo. For non-ionic surfactants, 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 temperatures (transitional phase inversion). During cooling, the system crosses a point zero spontaneous curvature and minimal surface tension, promoting the formation of finely dispersed oil droplets. Apart from temperature, salt concentration or pH value may also be considered. A transition in the radius of curvature can be obtained by changing the water volume fraction. Initially water droplets are formed in a continuous oil phase by successively adding water into

oil. Increasing the water volume fraction changes the spontaneous curvature of the surfactant from initially stabilizing a w/o microemulsion to an o/w microemulsion at the inversion locus[20]

Formulation considerations

The challenges in formulating topical microemulsions are:

1. Determining systems that are non-toxic, non-irritating, non-comedogenic and non-sensitizing.
2. Formulating cosmetically elegant microemulsions.

The microemulsion formulation must have low allergic potential, good physiological compatibility and high biocompatibility[22].

The components involved in the general formulation of microemulsions include (a) an oil phase (b) an aqueous phase containing hydrophilic active ingredients [preservatives and buffers may be included] (c) a primary surfactant [anionic, non-ionic or amphoteric] (d) secondary surfactant or cosurfactants[22].

Generally, non-ionic surfactants are chosen because of their good cutaneous tolerance, lower irritation potential and toxicity. Microemulsions can be formulated using single chain surfactants or double chain surfactants. Single chain surfactants do not lower the oil water interfacial tension sufficiently and hence cosurfactants are required. Double chained surfactants like sulfo succinates can form microemulsions in the absence of cosurfactants but are too 8 toxic for general pharmaceutical applications. The cosurfactants even though being indispensable in the formulation of exhibited toxicity e.g. 9 medium chain length alcohols. Hence judicious choice of surfactants and cosurfactants is of great importance. The use of polyoxyethylene alcohol ethers has been reported as cosurfacants. Microemulsions prepared from phospholipids such as lecithins are preferred over synthetic surfactants from the toxicity point of view . The biocompatibility requirements of the amphiphiles are fulfilled by lecithins and non-ionic surfactants (Brijs, Arlacel, Spans, Tweens and AOT)[22].

The following examples are commonly used formulations components of microemulsions

Oil:

The oil component influences curvature by its ability to penetrate and swell the tail group region of the surfactant monolayer. As compare to long chain alkanes, short chain oil penetrate the tail group region to a greater extent and resulting in increased negative curvature (and reduced effective HLB). Following are the different oil are mainly used for the formulation of microemulsion[20].

Saturated fatty acid-lauric acid, myristic acid, capric acid

Unsaturated fatty acid-oleic acid, linoleic acid, linolenic acid

Fatty acid ester-ethyl or methyl esters of lauric, myristic and oleic acid[20].

The main criterion for the selection of oil is that the drug should have high solubility in it. This will minimize the volume of the formulation to deliver the therapeutic dose of the drug in an encapsulated form[20]. Eg: Ethyl oleate, Mineral oil, Isopropyl myristate, Decanol, Oleic acid, Vegetable oils (Coconut oil, Safflower oil, Soyabean oil, Olive oil), Medium chain length triglyceride (Mygliol 812)[22].

Surfactant:

The role of surfactant in the formulation of microemulsion is to lower the interfacial tension which will ultimately facilitates dispersion process during the preparation of microemulsion and provide a flexible around the droplets. The surfactant should have appropriate lipophilic character to provide the correct curvature at the interfacial region. Generally, low HLB surfactants are suitable for w/o microemulsion, whereas high HLB (>12) are suitable for o/w microemulsion. Following are the different surfactants are mainly used for microemulsion.Polysorbate (Tween 80 and Tween 20), Lauromacrogol 300, Lecithins, Decylpolyglucoside (Labrafil M 1944 LS), Polyglyceryl-6-dioleate (PlurolOleique), Dioctyl sodium sulfosuccinate (Aerosol OT), PEG-8 caprylic/capril glyceride (Labrasol)[22].

Co-surfactant:[22]

Cosurfactants are mainly used in microemulsion formulation for following reasons:

- They allow the interfacial film sufficient flexible to take up different curvatures required to form microemulsion over a wide range of composition.
- Short to medium chain length alcohols (C3-C8) reduce the interfacial tension and increase the fluidity of the interface.
- Surfactant having HLB greater than 20 often require the presence of cosurfactant to reduce their effective HLB to a value within the range required for microemulsion formulation.

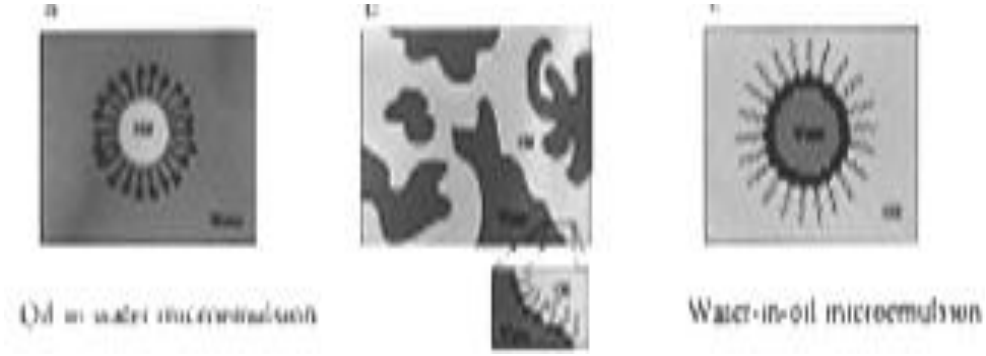

Figure 1 Types of Microemulsion

Following are the different cosurfactant mainly used for microemulsion: Sorbitanmonooleate, Sorbitanmonostearate, Propylene glycol, Propylene glycol monocaprylate (Capryol 90), 2-(2-ethoxyethoxy)ethanol (Transcutol P) and Ethanol.

Figure 2 A hypothetical pseudo-ternary phase diagram of an oil/surfactant/water system with emphasis on microemulsion and emulsion phases. Within the phase diagram, existence fields are shown where conventional micelles, reverse micelles or water-in-oil(w/o) microemulsion and oil-in-wter microemulsion are formed along with the bicontinuous microemulsion. At very high surfactant concentration two phase system are observed.

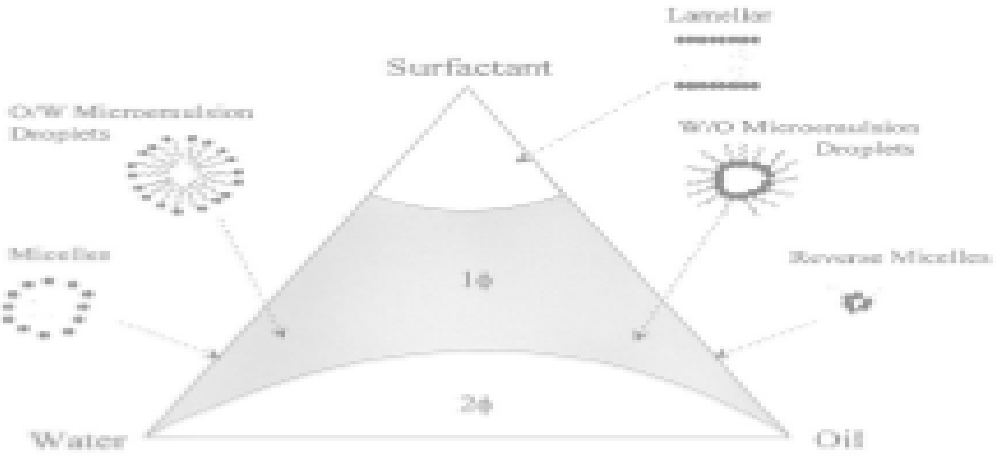

Figure 2 A hypothetical pseudo-ternary phase diagram

Hydrogel thickened microemulsion and it's advantages over microemulsion:-

The low viscosity of microemulsion restrains its application in pharmaceutical industry due to inconvenientuse[23]. Biocompatible hydrogels with weak interaction with surfactants have recently been found to change the rheology properties of microemulsion. The addition of hydrogels, e.g. carragenan and carbomer 940 into microemulsion resulted in the formation of hydrogel-thickened microemulsion with a weak gel behavior and the change of viscosity . However, there is lack of the direct observation of the microstructure of microemulsions combined with hydrogels, even though the properties of microemulsions combined with hydrogels implied that the oily phase might be hosted within the three-dimensional gel network or microemulsions transformed to lamellar structure or a highly ordered microstructure[25-26]. Additionally, the influence of the incorporation of hydrogels into microemulsion on the permeation ability of microemulsion to deliver drug through skins is unexplored. The hydrogel-thickened microemulsion (HTM) system with a high viscosity and powerful permeation ability is expected to deliver an extremely low concentration of drug[24].

CONCLUSION:

This article described about the Rheumatoid arthritis an auto immune disease and NSAID as a drug of choice in Rheumatoid arthritis. It elaborately described about topical route of drug delivery. This article also describes about microemulsion and hydrogel thickened microemulsion along with references was cited at the end of the chapter.

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