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Review Article

Review on a Thermodynamically Stable Nanolipoidal Drug Delivery System

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ABSTRACT

The poor pharmacokinetics of many pipeline medication candidates prevent them from ever reaching the market. The progressively low bioavailability of the recently studied New Molecular Entities (NMEs) is one such obstacle in the medication development process. Formulators frequently use the nano-lipoidal colloidal system, which creates micro-emulsions and nano-emulsions as drug delivery vehicles for BCS Class II, III, and IV medications, as a promising platform to address such bioavailability problems. Owing to the coexistence of surfactants and hydrophilic and lipophilic domains, these nano lipoidal colloids demonstrate superior drug solubility and permeability across biological environments. Micro-emulsions are mixtures of water, oil, and surfactant plus a co-surfactant that are isotopically transparent and thermodynamically stable. Micro-emulsions can reduce patient variability in pharmacokinetics and therapeutic action, protect labile drug ingredients, control drug release, increase drug solubility, increase absorption followed by bioavailability, reduce medication dose and limit toxicity. The devices can be utilized as Self-Micro-emulsifying Drug Delivery Systems (SMEDDS) to provide medication orally in order to prevent drug hydrolysis while being stored and to minimize bulk.

INTRODUCTION

Pharmaceutical research is constantly designing and developing new drug delivery systems with the goal of improving the efficacy of already-existing therapeutic molecules. Dosage Form Design Considerations, 2018 estimates that 90% of medications are taken orally. After a medication is given, absorption occurs first and is dependent on solubilization and then penetration. Because of their poor permeability and low solubility, over 40% of Investigational New Drugs (IND) are removed from the development pipeline [1]. There is a lot of optimism for the therapeutic usage of those poorly bioavailable medications with the nano-lipoidal system. The focus of current research is on using a thermodynamically stable

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nano-lipoidal system to increase the bioavailability of drugs that are not very bioavailable. The pharmaceutical industry is constantly formulating and developing new drug delivery systems to boost the bioavailability of currently available medications. Considering the vast array of drug delivery technologies that have been created. Hoar and Schulman first proposed the idea of micro-emulsion in the 1940s; they did this by utilizing hexanol to triturate a milky emulsion and creating an optically clear single-phase solution [2]. We can now apply the definition provided by Attwood, which states that a micro-emulsion is a system of water, oil, and amphiphilic compounds (surfactant and co-surfactant), which is a transparent, single optically isotropic, and thermodynamically stable liquid. This structure was established through the use of various technologies. The word "micro-emulsion" refers to a dispersion of two or more immiscible liquids, such water and oil, that is thermodynamically stable, isotopically transparent, and stabilized by an interfacial coating made up of one or more surfactant molecules. Molecules of surfactants have both lipophilic and hydrophilic groups. Thus, they behave in a very strange way. Initially, they adsorbed at the interface, where they could satisfy their twofold attraction for lipophilic groups found in the oil or air phase and hydrophilic groups found in the watery phase. Second, through the production of micellization, they lessen mismatching with solvent. The dispersed phase has a very low oil/water interfacial tension and usually consists of minute particles or droplets that range in size from 5 to 200 nm. Micro-emulsions are optically clear transparent systems because the droplet size is less than 25% of the visible light wavelength [3-5]. Micro-emulsions are continuous systems consisting of bulk phases of oil and water divided by an interfacial area rich in surfactants and co-surfactants [6]. The fact that these systems are liquid systems with thermodynamic stability gives them an edge over traditional emulsions [7]. Since micro-emulsions have so many real and potential applications, numerous researchers are now studying them. Pharmaceutical companies find micro emulsions to be attractive formulations due to their great carrying capacity for both hydrophilic and a hydrophobic drug delivery. Additionally, these systems have a number of advantages for oral administration, such as enhanced clinical potency, reduced dosage-related toxicity, and enhanced absorption and bioavailability of poorly soluble medications. [8]

Table1: Basic differences between Emulsion and Micro-emulsion [9-11].

Sl. No	Emulsion	Microemulsion
i.	They are lyophobic in nature	They are intermediate of lyophobic and lyophilic.
ii.	Droplet diameter ranges from 1 to 20 mm.	Droplet diameter ranges from10 to 100nm.
iii.	Emulsion droplets exist as individual entities.	Micro-emulsion droplets disappear within fraction of seconds.

Advantages of microemulsion system- a. Micro-emulsions are simple to prepare and consume very little energy, which contributes to the preparation's thermodynamic stability.

b. The process of micro-emulsion production is reversible. They may become unstable at low or high temperatures, but they reorganize to form a micro-emulsion when the temperature returns to its stability range.

c. The system can self-emulsify because of the temperature stability of micro-emulsions.

d. In comparison to macro-emulsions, micro-emulsions are less viscous.

Disadvantages of micro-emulsion systems [12-14]

a. Having partial solubilizing capacity for high melting substances.

b. Require bulk of Surfactants for stabilizing droplets.

c. Microemulsion stability is influenced by environmental parameters such as temperature and pH.

2. **Types Of Microemulsion**

The types of microemulsion include

a. oil in water type (O/W), b. water in oil type(W/O), and c. bicontinuous type. Oil in water type:Droplets of oil scattered across a continuous phase of water and encased in a coating of surfactant-cosurfactant. Given that water is the exterior phase, they show a higher interaction volume. The surfactant monolayer's interfacial film has a positive curvature. The lipophilic non-polar tails are oriented in close proximity to the internal phase of oil, whereas the hydrophilic polar heads face the external phase of water [18, 19]. Water in oil type: In the exterior oily phase, droplets of water are distributed. Because of the way that their polar heads and fatty oil chains are oriented, they are known as "reverse micelles. “The w/o emulsions can be destabilized by aqueous biological systems through an increase in the internal phase's phase volume. The percolation phenomenon finally causes phase inversion or phase separation [18, 19]. Bi-continuous type: Bicontinuous emulsions are created when the content of water and oil is equal. In this system, the phases of water and soil coexist continuously. The overlapping of asymmetrical oil and water channels gives the appearance of a "sponge phase." Their non-Newtonian flow and flexibility are beneficial for the topical or intravenous administration of medications [18–19].

2.1. Winsor classification of micro-emulsion[20]

Winsor classified phase equilibrium into four types based on phase behavior of water-oil-surfactant mixtures in the commonness of diverse additives as shown Fig. 1.They are,

I. Oil- in- water micro-emulsion or Winsor I type system
II. Water-in-oil micro-emulsion or Winsor II type system
III. Bicontinuous micro-emulsion or Winsor III type system

Single phase homogeneous mixture or Winsor IV type system

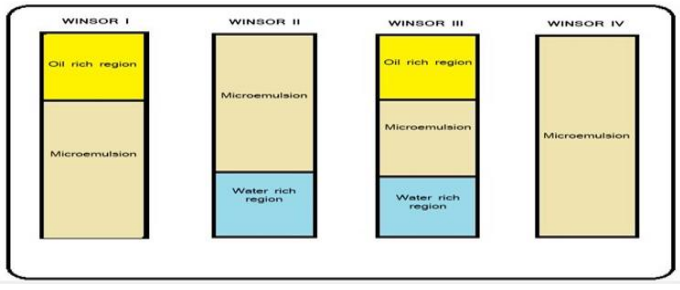

Fig. 1. Schematic presentation of Winsor classification of microemulsion

I. Oil- in- water types micro-emulsion or Winsor I type system: Oil droplets in Winsor I type micro-emulsions are surrounded by a continuous phase, the internal phase, which is spread in water and is composed of a mixture of surfactants and co-surfactant film. Compared to w/o micro emulsions, this kind

of micro emulsion often has a larger interaction volume.

II. Water - in - oil micro-emulsion or Winsor II type system: Water droplets in this kind of micro-emulsion are restricted by an ongoing oil phase. These are referred to as "reverse-micelles," in which the non-polar tails of the surfactant face into the oil phase while the polar head groups of the surfactant are fronting the water droplets. In the aqueous biological system, a w/o micro emulsion administered orally or parenterally may be diluted.

III. Bicontinuous micro-emulsion or Winsor III type system: Water and oil are present in an unequal proportion in a bicontinuous microemulsion system; in this instance, they coexist as a continuous phase. An uneven network of water and oil joins, and a structure resembling a "sponge phase" emerges. During this bicontinuous phase, Winsor I to Winsor II micro-emulsion conversions takes place. Bi-continuous micro-emulsion is typically followed by non-Newtonian flow and plasticity. These characteristics make them particularly helpful for both intravenous and topical medication delivery.

IV. Single phase homogeneous mixture or Winsor IV type system: In single phase homogeneous types mixture or Winsor IV type system the oil, water and surfactants are mixed simultaneously. These types of systems are generally shaped by changing the curvature of interface by the assist of various factors such as salinity, temperature, etc.

2.2 Prediction of the type of micro-emulsion

a. Bancroft attempted: utilizing the emulsifier to forecast the kind of microemulsion. Water-soluble emulsifiers form an o/w micro-emulsion, while oil-soluble emulsifiers form a w/o microemulsion, according to Bancroft's rule.

b. Role of critical packing parameter (CPP**):** Surfactants possess head and tail that affect the curvature of the interface (Fig.2). In 1976, Israelachvii proposed a relationship between the head group area (ao) and the tail effective surface area(v/lc), where*v*is the volume and lc is the effective hydrocarbon chain. By this geometrical equation, the Critical Packing Parameter (CPP) is stated as CPP = v/lcao……. (1)

Theoretically, the value of CPP is less than 1/3 corresponds to spherical micelles, and value in between 4 /3 and 1/2 corresponds to rod like micelles and between 1/2 and 1 to a planar structure (Fig. 3) [21].

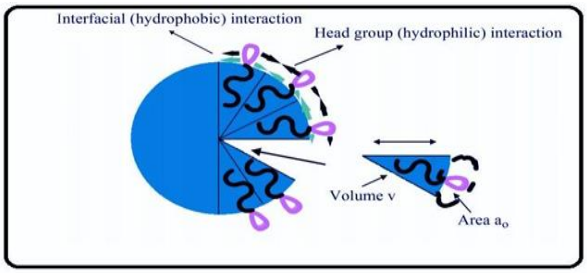

Fig. 2. Surfactant aggregate structure for critical packing parameters (CPP) from < 1/3(lower left) to >1 (upper right)

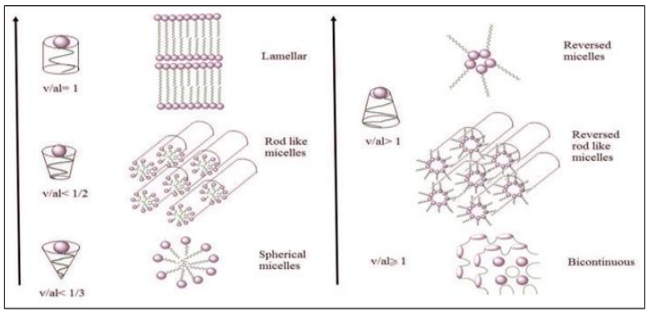

Fig. 3. The carbon chain's head group area, length, and volume are related to a dimensionless number by the crucial packing parameter.

c. Role of Mean curvature of surface (H):

The value of the surface mean curvature can be used to distinguish between different types of emulsion. Where "a" is the radius of the dividing surface, H=(-1/a) for the water/oil interface and (1/a) for the oil/water interface. Therefore, a negative value for H implies that an emulsion is water in oil, whereas a positive number suggests that the emulsion is oil in water.

d. Role of Thermodynamic free energy(ΔG):

Figure 4 shows the quantitative result of this model for specific free energy as a function of droplet size. Only in the case of emulsions does the change in free energy always result in a positive change. This is the case when B and C are involved. As a result, in the C-zone, thermodynamically unstable emulsions occur. However, depending on the energy barrier, kinetically stable emulsions could occur. When the free energy change is negative up to a specific radius (R) of the dispersed phase, it means that the micro-emulsions that are generated are thermodynamically stable and that the droplets with a radius within this size range are stable towards phase separation. The computations show that by lowering specific surface free energy, surface potential and particular composition are what cause the curves to change from C to A.

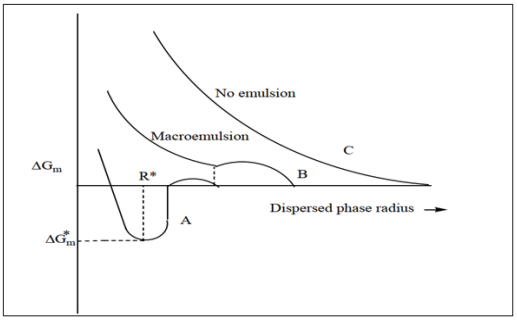

Fig. 4. Diagrammatic illustration of free energy as a function of droplet size

3.Composition Of Microemulsion

A variety of components are used in the creation and formulation of the microemulsion system. In order to prepare a microemulsion, mostly oil, surface-active agent, and co surfactant mixture are used; these ingredients must be inexpensive, biocompatible, non-toxic, and clinically acceptable [21]. Main elements of microemulsion are

a. Oil phase d. co surfactant
b. Aqueous phase
c. Surfactant

a. Oil phase: Oil is a necessary component of a microemulsion because it increases the amount of lipophilic medicine transported through the internal vascular system and aids in solubilizing the desired dose of the lipophilic drug. Any liquid with low polarity and low water miscibility is classified as oil. Oil phase is essentially composed of medium or short chain fatty acids. Some oil

phases include mineral oil, toluene, cyclohexane, edible oil, etc. [21, 22].

b. Aqueous phase: Typically, the aqueous phase is helps to binds hydrophilic active ingredients and preservatives. Buffer solutions are sometimes used as aqueous phase. [21]

c. Surfactant Surfactants are surface-active agents that reduce surface or interfacial tension and can dissolve both polar and non-polar solvents. These molecules have a polar head and a non-polar tail, enabling self-association due to molecular interactions and entropy. In systems like oil and water, surfactants align at interfaces, forming structures such as micelles (spherical, rod-shaped, or reverse), lamellar sheets, or hexagonal phases. At low dispersed-phase concentrations, microemulsions with spherical droplets may form. Four main types of surfactants exist, some of which aid in microemulsion development.[22,23]

i. Cationic

ii. Anionic

iii. Non-ionic

iv. Zwitter ionic surfactants.

i. Cationic surfactant: Cationic Surfactants when arise in contact with water droplets, they converted into amphiphilic cation and anion form, most often of halogen type. Some examples of cationic surfactant in clued Nitrogen compounds such as quaternary ammoniums and salts of fatty amine, long chain of the alkyl group etc. The most well-known examples of cationic surfactant class are hexadecyl trimethyl ammonium bromide and dodecyl ammonium bromide. These surfactants are in generally more expensive than anionics [21,23].

ii. Anionic surfactant: When anionic surfactants are comes in contact with water dissociation occurs and they produce an amphiphilic anion, and a cation, an alkaline metal (Na, K) or a quaternary-ammonium. These are widely used surfactants. The ionized carboxyl group (COO) is responsible for the negative charge in these surfactants. Anionic surfactants of about 50 % are used worldwide for production. Alkalialkenoates, known as soaps, are the most commonly used anionic surfactants. This is the most familiar type of surfactant when it comes to their shape and the function. Carboxyl ate, sulfonate and sulphate groups are most important anionic groups in all of these surfactants [24].

iii. Non-ionic surfactant: Non-ionic surfactant is stable due to the formation of dipole and hydrogen bonding interactions with hydration layer of water at its hydrophilic surface. They do not undergo ionization in aqueous solution, because they have non-dissociable hydrophilic group, such as phenol, alcohol, ester, or amide. Due to presence of polyethylene glycol chain, they made it more hydrophilic [21, 24].

iv. Zwitter ionic surfactant: In zwitterionic surfactants both positively and negatively charged groups are present and form micro-emulsions by addition of co-surfactants. Phospholipids, such as lecithin from soybean or egg are common example of zwitterionic surfactants [25]. Lecithin contains diacyl phosphatidylcholine isconsideredas the major constituent that also have excellent biocompatibility. Other important class of zwitterionic surfactants includes betaines, such as alkyl betaines, and heterocyclic betaines [21-23].

d. Co-surfactant**:** It has been experienced that a single-chain surfactants not have enough interfacial tension reducing capability to form a microemulsion. The addition of co-surfactants makes the interfacial film to be more flexible to absorb different curvatures to form micro-emulsion with wide range of excipients. The usage of co-surfactant is to abolish liquid crystalline or

gel structures that come in place of a micro-emulsion phase during formulation [23]. Co-surfactants are used in the formulation of microemulsion for the following reasons:

- They permit the interfacial film adequate flexible to produces different curvatures that is required to form micro-emulsion with wide range of excipients.
- Short to medium chain length alcohols (C3-C8) have the ability to reduce the interfacial tension and increase the flexibility of the interface [25].
- Sometimes surfactant with a HLB value greater than 20 often need a co-surfactant to reduce their effective HLB to form a stable micro-emulsion formulation [26].

Following are the different co-surfactant mainly used for microemulsion: Tween20, Span20, propylene glycol, propylene glycol monocaprylate (Caproyl 90), 2-(2-ethoxyethoxy) ethanol (Transductal) and ethanol [21, 25].

4. Theories Of Microemulsion Formation

The formulation of micro-emulsion is constructed on various theories that effect and control their stability and phase behavior [27]. These theories are

A. Thermodynamic theory
B. Solubilization theory
C. Interfacial theory

Thermodynamic theory- The thermodynamic study of micro emulsions explores droplet size and stability, emphasizing that spontaneous formation occurs when the free energy of mixing (ΔGm) is negative. Stability depends on variables like interfacial and droplet clustering energy, with reduced interfacial tension (10^{-4} to 10^{-5} dynes/cm) facilitating formation. Key factors include van der Waals forces, electric double layers, entropic contributions, and surfactant concentration, which lowers surface tension and drives entropy changes. Microemulsions are more complex than macro emulsions, with stability influenced by molecular interactions, interfacial charge, and thermodynamic variables, as quantitatively described by Gibbs free energy analysis.[28,29]

Thus, $DGf = \gamma DA - T\,DS$

Where,

DGf= Free Energy of micro-emulsion formation,

γ = Surface Tension of oil-water interface,

DA = Change of the interfacial area during micro-emulsification,

DS = Change in entropy of the system.

T = Temperature.

When the formation of micro-emulsion is done, DA automatically increases due to increases the effective area by broken down of droplets into very small fragments. Most important things that always keep in mind, the value of γ must be positive. The dominant favorable entropic contribute during the mixing of one phase into another and helps to formation of large numbers of small droplets. However, favorable entropic contributions also come from other dynamic processes such as monomer-micelle surfactant exchange and surfactant diffusion in the interfacial layer [27-29].

B. Solubilization theory**:** Solubilization theory states that the formation of micro-emulsion of polar and non-polar phase twitch by the formation of micelles or reverse micelles. Further these micellar molecules well and gradually become larger in size [28].

C. Interfacial theory: According to this theory a spontaneous negative interfacial tension between the surfactant and co surfactant molecules occurs in microemulsion system. The film made of surfactant as well as co-surfactant molecules, considered as a liquid ‘‘two dimensional’’ equilibrium phase system [27]. These types of monolayer film may be formed a duplex film, i.e. they showed different types of properties on both water side and oil side. According to the duplex-

film theory, interfacial tension (γT) is express by the following expression [28-29]

$\gamma T = \gamma(O/W) --- \pi$

Where,

γ (O/W) a = Interfacial Tension. T=Temperature.

5. Method Of Formulation

When in an oil- When the interfacial layer is sufficiently flexible and the concentration of surfactants is sufficient to achieve an extremely low interfacial tension, the interfacial tension between the water molecules and the oil molecules in the water system will be reduced, resulting in the spontaneous formation of micro-emulsions [30].

Two main methods are reported to the formulation of micro-emulsion, these are

i. Phase Inversion Method

ii. Phase Titration Method

Phase Inversion Method: Phase inversion in micro emulsions occurs with excess addition of the dispersed phase, causing rapid changes in particle size and drug release profiles. For non-ionic surfactants, phase transitions between oil-in-water (O/W) and water-in-oil (W/O) microemulsions are temperature-dependent, with the phase inversion temperature (PIT) marking minimal surface tension and small oil droplet formation. Factors like pH, salt concentration, and water volume fraction also influence phase inversion. Gradual water addition to an oil phase leads to a transition in curvature, shifting from W/O to O/W microemulsions at the inversion point.[31, 32] (Fig.5).

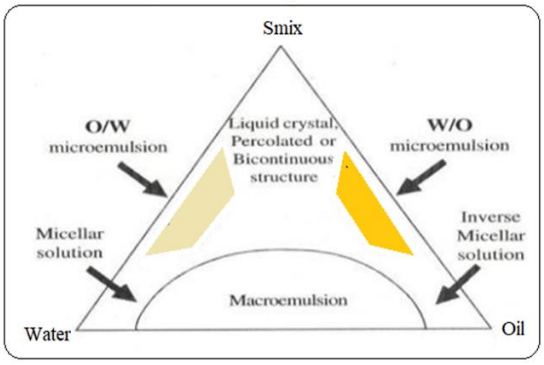

Fig. 5: Hypothetical Phase region of Micro-emulsion system Of oil, water and surfactant co-surfactant mixture (Smix)

From the above Fig.5, we can see that,

- When concentration of oil, surfactant is high, forms reverse micelles capable of solubilizing more water molecules in their hydrophilic interior.
- Formation of W/O micro-emulsion occurs due to the addition of water gradually in which water exists as droplets surrounded and stabilized by interfacial layer of the surfactant / co-surfactant mixture.
- At a minimal water content, the isotropic clear region changes to a turbid one.
- Additional dilution with water further formed a liquid crystalline region in which the water become sandwiched between surfactant double layers.At finally stage when amount of water increases, this lamellar structure will break down and water will form a continuous phase.

i. Phase Titration Method:

Micro-emulsions are formulated by the spontaneous emulsification method (phase titration method) and further developed with the help of phase diagrams. When a mixture of fatty acid and oil is added to a caustic solution formation of micro-emulsion begins, then addition of a co surfactant (an alcohol), the system turned visually transparent. Formation of micro-emulsions occurs

with the creation of numerous structures (such as emulsion, micelles, hexagonal, cubic, and several gels and oily dispersion), it depends upon chemical constituents and concentration of individual component. Significant transmittances of visible spectrum can be formed with addition of longer chain oils a surfactant in micro-emulsion. It is found that different alcohols are responsible to affect the construction of micro-emulsions in so many ways. The best results, in terms of the highest percent transmittance are obtained by formulate the preparation with short or branched chain oils, surfactant and co-surfactant (alcohols) [32-33] (Fig.6).

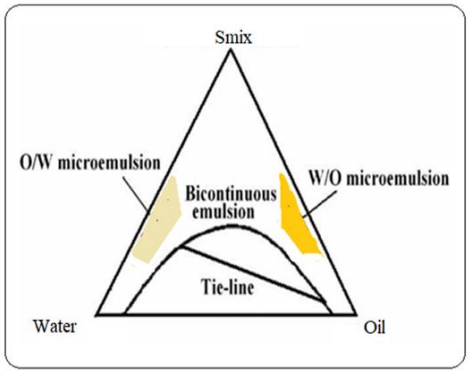

Fig. 6: Pseudoternary phase diagram of oil, water and surfactant co-surfactant mixture (S mix) showing micro-emulsion region

5.1. Case Study:

A case study on "Studies on a thermodynamically stable nano lipoidal system for a poorly bioavailable drug (valsartan)" was discussed here

Table2: List of Materials used for Formulation

Materials used		Manufacturer	Composition/Types
Drug	Valsartan	Gifted from Mylan Laboratories Limited, AP, India	Valsartan EP
Oils	Soya bean oil	Fortune Refined, Adani Enterprise Limited, Ahmadabad	Food grade oil
	Sunflower oil	Agro Tech Foods Ltd., Kolkata	Refined Food Grade
	Saffola oil	Marico Limited, Mumbai	80%Refine dricebran & 20% Refined Safflower oil
	Olive oil	Borges India Private Ltd., New Delhi	Extra Virgin
Surfactant/ Cosurfactant	Tween 20	Nice Chemical Private Limited, Kerala	Polyoxyethylene monolaurate
	Span20	Nice Chemical Private Limited, Kerala	Sorbitan monolaurate
	Tween80	Nice Chemical Private Limited, Kerala	Polyoxyethylene sorbitan monooleate
	Isopropyl Alcohol	Nice Chemical Private Limited, Kerala	----------
	Glycerin	Scottish Healthcare, Rajasthan	----------

Table3: List of Equipment used for Formulation

Equipment	Model Number	Manufacturer
Micropipette	Micro-pipette (10-100µl)	Micro-lit, Lucknow.
Vortex Mixer	Cyclo mixer (CM 101)	REMI, Mumbai
UV/VIS Spectrophotometer	UV-1800	Shimadzu Corporation, Japan
Digital Balance	MettlerToledo-ME204/A04	Mettler Toledo,USA
Melting Point Apparatus	Digital Automatic Melting Point Apparatus CL725	Labline Technologies Pvt Ltd.

5.1.2. Methodology:

5.1.2.1. Physicochemical Study of the Drug:

a. Melting point determination: Melting point isa unique property of any solid substances. This is the temperature at which liquid and solid can co-exist at equilibrium. Here for the purpose of study a digital automatic melting point apparatus, CL725 was used to determine the melting point of pure drug (valsartan) in triplicate.

b. UV-visible spectrum: Maximum absorbance at a particular wave length (λmax) was determined by scanning the standard solution of the drug at a wavelength of 400-200 cm^{-1} by using Shimadzu UV-1800 Spectrophotometer.

c. Standard Curve preparation of Valsartan EP: 10 mg of drug was taken and dissolved in ethanol up to the volume of 10 ml to prepare stock solution of 1000ppm. Then 1ml of stock solution was taken and diluted with ethanol up to 10 ml to prepare 100ppm solution. From this 0.2, 0.4, 0.6, 0.8, 1, 1.2, 1.4 ml was taken by the help of a micro-pipette and dilute with up to 10ml of ethanol to get standard solution of 2ppm, 4ppm…14ppm.

5.1.2.2. Formulation

a. Screening of surfactant and Co-surfactant: A series of surfactant and co-surfactant with different HLB values and mutual solubility have been screened such as Tween 20, Tween 80, Span 20, Span 80, Glycerol, Isopropyl alcohol, and we found that Tween 20 and Span20 with Saffola oil showed best combination for developing micro-emulsion system.

b. Miscibility study: Miscibility study of surfactant and co-surfactant mixture(Smix)with oil phase was performed to check the formulation compatibility.

c. Construction of pseudo ternary phase diagram: Pseudoternary phase diagram was constructed using aqueous titration method to examine the formation of micro-emulsion using three components oil, surfactant & co-surfactant mixture (Smix) and dilution with distilled water. The three-component system consisted of oil as Saffolaoil, surfactants as Tween 20 and a co-surfactant Span20. These components have been taken on weight basis. Pseudo ternary phase diagram was constructed varying the ratio of Oil and the Smix of different ratio(1:9to9:1).Various ratios of Tween 20 and Span20(1:1,2:1) were prepared to get the best for formulating the model drug in the micro-emulsion system which can be clear and transparent on dilution with water and hence, the final diagram was constructed varying the oil and Smix ratio[Tween 20**:**Span20=2**:**1] that was generated using *ProSim*Software.

5.1.3. RESULTS AND DISCUSSION

A. Pre-formulation study of Valsartan EP:

a) Melting Point: Here, for the study Digital Automatic Melting Point Apparatus CL725 was used.

Table 4: Melting point of valsartan

Standard melting point [33]	**Observed melting point**
116-117ºC	115-116ºC

b) UV Spectrum: Here, for the study Shimadzu UV-1800 Spectrophotometer was used.

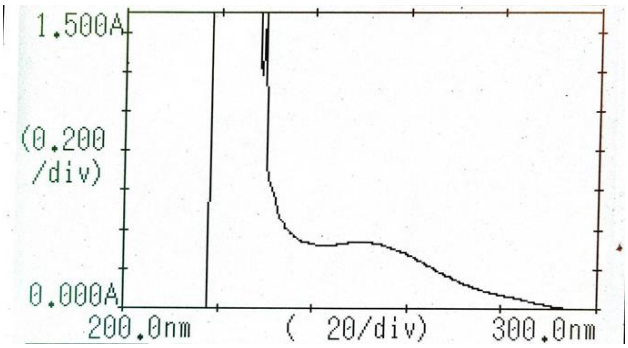

Fig. 7. UV spectrum of Valsartan EP in ethanol

Table5: Maximum wavelength (λmax) of Valsartan EP in ethanol

Standard λ max [33]	**Observed λ max**
249±0.5nm	248.5nm

Table 6: Data for Standard Curve of Valsartan EP in ethanol

Sl. No	**Concentration(ppm)**	**Absorbance**
1.	0	0
2.	2	0.195
3.	4	0.41
4.	6	0.573
5.	8	0.79
6.	10	0.98
7.	12	1.18
8.	14	1.38

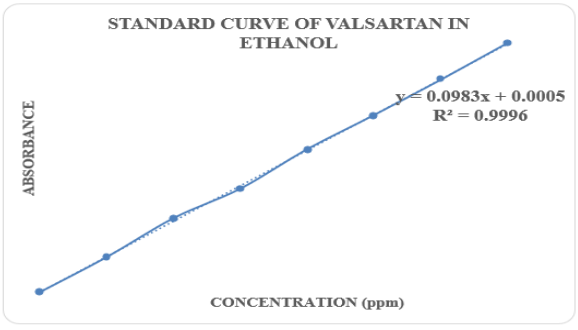

Fig. 8. Standard curve of Valsartan in ethanol

5.2.2. Screening of Oil, Surfactant and Cosurfactant

Table 7: Data for mutual miscibility of oils, surfactant and co-surfactant

Sl. No	Ingredients	Ratio	Observation
1.	Sunflower oil + Tween 20	1:1	Separate into two layers
2.	Sunflower oil + Tween 20+ Isopropyl alcohol	1:1:1	Separate into three layers after 4 hrs.
3.	Olive oil + Tween 20 + Span 20	1:1:1	Separate into two layers
4.	Olive oil + Isopropyl alcohol + Tween 20	1:1:1	Separate out after 2 hrs.
5.	Saffola oil + Tween 20 + Isopropyl alcohol	1:1:1	Primarily miscible but separate into two layers after 24 hrs.
6.	Saffolaoil +Tween 20 + Span20	1:1:1	Miscible
7.	Saffolaoil +Tween 20 + Span20	1:2:1	Highly miscible
8.	Saffola oil + Tween 20 + Glycerol	1:1:1	Primarily miscible but separate into two layers.
9.	Saffola oil + Tween 20 + Span 20	1:1:2	Gel formation occurs

A range of surfactants and co-surfactants, including Polyoxyethylene sorbitan monolaurate (Tween 20), Span20, Glycerol, Isopropyl Alcohol, and Sorbitan monooleate (Span 80), were screened for their HLB values and mutual solubilities. The results indicated that the optimal combination for creating the model drug in a microemulsion system was Tween 20 plus Span20. In the meanwhile, we added several oils (olive, sunflower, saffola, soybean, and sunflower) in varying amounts of co-surfactants and surfactants.

5.2.3. Construction of Pseudo ternary Phase Diagram

Table 8: Data for Pseudo Ternary Phase Diagram of Smix ratio 1:1(Oil= Saffola oil, Smix= Tween 20 & Span 20)

Sl. No	Oil: Smix ratio	% Of Oil	% Of Smix	% Of Water
1.	9:1	88.62	10.3	1.08
2.	8:2	76.2	18.3	5.5
3.	7:3	67.5	26.4	6.1
4.	6:4	56	32.8	11.2
5.	5:5	39	39	22
6.	4:6	26	17	57
7.	3:7	7	11	82

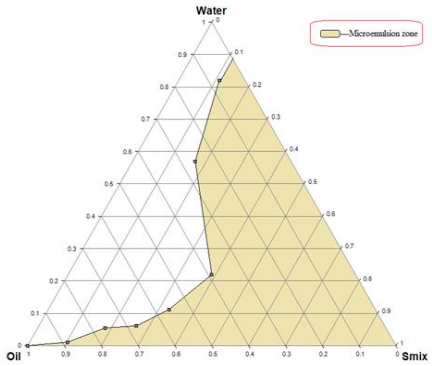

Fig-9: Pseudo ternary Phase Diagram for Smix ratio 1:1 (Oil= Saffola oil, Smix= Tween 20 & Span 20)

Table 9: Data for Pseudo Ternary Phase Diagram of Smix ratio 2:1(Oil= Saffola oil, Smix= Tween 20 & Span 20; %w/w)

Sl. No	Oil: Smix ratio	% Of Oil	% Of Smix	% Of Water	Total %
1.	9:1	85	9.5	5.5	100
2.	8:2	67.61	17.4	15	100
3.	7:3	57.66	26.04	16.3	100
4.	6:4	52.9	32.7	14.4	100
5.	5:5	35.4	35.4	29.2	100
6.	4:6	20.9	28	51.1	100
7.	3:7	3.2	17.3	79.5	100

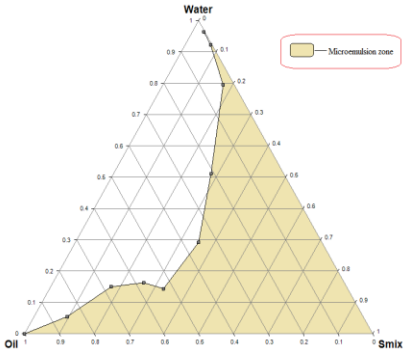

Figure.10: Pseudo ternary Phase Diagram for Smix ratio 2:1 (Oil= Saffola oil, Smix= Tween 20 & Span 20)

The conventional pseudo ternary phase diagram was used in conjunction with the water dilution technique to establish an acceptable formulation system for micro-emulsions. Initially, oil was combined with co-surfactant mixture (Smix) and surfactants on a weight basis. This combination was then vortexed, and water was added until the transition point, which is when the emulsion's clarity changed from clear to milky. In order to obtain a wider zone for forming the model medication in the system, phase diagrams were generated by adjusting the ratio of Saffolaoil and Surfactant mixture of different ratios, such as Tween 20 and Span20 in a ratio of 1:1 and 2:1. A pseudo-ternary diagram was created using Pro Sim. The larger zone for maximum drug loading in the system was discovered to be provided by the Smix ratio Tween20: Span20 of 2:1.

6. Factor Affecting Formulation Of microemulsion System

6.1. Property of surfactant: Surfactant contains both lipophilic and hydrophilic groups and depending upon the nature of surfactant stability as well as thickness altering. For example, when single hydrophilic chain surfactants (cetylethyl-ammonium-bromide) added into microemulsion system dissociation occur and produce a o/w microemulsion. [34,35].

6.2. Nature of Co-Surfactant: In the formation of microemulsion shorter chain surfactant(alcohols)are most widely used co-surfactant in micro emulsions formulation. Alcoholbindwiththeheadregionofsurfactantandres ultingtotheswellingofheadregionthatgives positive curvature effect and o/w type is microemulsion is formed, while longer chain co-surfactant have a tendency to form w/o type microemulsion [36].

6.3. Property of Oil Phase:

Changing the curvature of micro emulsion depend supon the penetration & swelling fficacy of the tail group of surfactant layer swelling of tail resulting an increasing of negative curvature that formed w/o microemulsion [37].

6.4. Packing Ratio**:** Types of micro-emulsion formation is depending upon the HLB value of surfactant and are responsible for the influence of packing ratio and film curvature of micro-emulsion system. [38].

6.5. Temperature: Size of effective head group changes with changing into the temperature. Head groups are hydrophilic at allow temperature and form o/w microemulsion system and at higher temperature, they formed w/o micro-emulsion systems [36, 38].

7. Evaluation Of Microemulsion System-7.1. Physical appearance: Physical appearance of microemulsion can be examine visually to check homogeneity, fluidity as well as optical clarity [39].

7.2. Phase Behavior Studies: Study of phase behavior is most important parameter stop redact microemulsion system by the help of phase diagram that give an information about the different phases as a function of composition variables and temperatures, and, more importantly structural organization of the system. Phase behavior studies also help to compare the efficiency of different surfactants. To understand about phase behavior, simple equipment's are used that easily measure there querulent. The borders of one-phase region can be measured easily by visual observed by known composition sample [39, 40].

7.3 X-rayScattering Techniques: Scattering techniques, including small-angle neutron scattering (SANS), small-angle X-ray scattering (SAXS), and light scattering techniques, are employed to investigate the structure of micro emulsions. To minimize inter-particular interactions, it is often necessary to dilute the sample. However, such dilution can alter the structure and composition of the pseudo phases. SAXS is particularly useful for obtaining information about the size and shape of droplets within the microemulsion. Light scattering techniques are widely used to determine the droplet size and shape by measuring the intensity of scattered light at various angles and concentrations of the microemulsion solution. Dynamic light scattering (DLS), also known as photon correlation spectroscopy (PCS), is used to evaluate changes in intensity resulting from the Brownian motion of the system.[41-43].

7.4. Nuclear Magnetic Resonance Studies**:** To determine the structure and dynamics properties of micro-emulsions nuclear magnetic resonance (NMR) techniques is very useful tools. Self-diffusion measurements of micro-emulsion droplets is done by using different tracer techniques including radio labeling that gives an idea about the flexibility of the components. The Fourier transform pulsed-gradient-spin-echo (FT-PGSE) technique is also useful, it allows simultaneously rapid determination of the self-diffusion coefficients (10^{-9} to $10^{-12}m^2S^{-1}$), of many components by the help of magnetic gradient of the samples [41,43].

7.5. Limpidity Test (Percent Transmittance): Limpidity is an appropriate level to check impurities by the help of UV-spectrophotometer, determine the percent transmittance, this percent transmittance is directly proportionate with limpidity [42, 47].

Table 10: Some Reported Absorbance for Limpidity studies

Serial No	Drug	Absorbance(nm)
1	Quetiapine Fumarate	650[48]
2	Bifonazole	630[49]
3	Paclitaxel	633[50]
4	Nebivolol	650[51]

7.6. Stability Study: Three distinct temperatures are maintained for the prepared micro-emulsion: room temperature (20–25°C), cold temperature (4–8°C), and higher temperature (50 ± 2 °C). Phase separation, globule size, and percentage transmittance were then assessed for the

microemulsion at intervals of two months during a one-year period. The test was also evaluated to see whether any changes in product quality occurred. Freeze-Thaw Cycles (FTC) are when the mat is kept at 25° C for 24 hours and then again for another 24 hours if they pass [44].

7.7. Globule size and zeta potential measurements: By using dynamic light scattering technique and help of Zettaliter HSA 3000 globule size and also the zeta potential of microemulsion system is determined [44].

7.8. Viscosity measurement: Viscosity is one of the key rheological characteristics that affects a liquid biphasic system's stability. The viscosity is often measured using a Brookfield digital viscometer, which distinguishes the microemulsion zone from other regions [45].

7.9. Electrical conductivity: Microemulsions can be differentiated based on electrical conductivity. In case of o/w systems, a phenomenon called PERCOLATION effect is exhibited, when a fraction of dispersed phase volume(φ) is increased. The electrical conductivity is very sensitive that leads to the aggregation of droplets and they suddenly extent up to several orders of magnitude due to the continuous electron paths or conducting networks formation. This effect is reported by various researchers in their studies. A paper Leagues, firster ported the dramatic increase of the conductivity with increase the fraction of droplet volume for a water-in-oil microemulsion in terms as percolation model and coined out situation as stirred percolation, that occurs due to the Brownian motion of the medium, wherein the conductivity of the microemulsion far exceeds the conductivity of the aqueous phase used [8,43,45,47].

7.10. Electron Microscope Characterization: Transmission Electron Microscopic technique (TEM) is a very informative tool to study the internal structures of micro-emulsions. There are two variations of TEM technique are available for fluid samples.

1. The cryo-TEM analyzer, where the samples are directly visualized.
2. The Freeze Fracture TEM technique in which a copy of sample is visualized [44].

7.11. Isothermal Titration Calorimetry (ITC): Isothermal titration calorimeter is used to measure changes in the enthalpy of mixing (M_{ix}). Determination of the enthalpy change makes it conceivable to describe about the molecular interaction of internal energy, aim to determine the effect of temperature on dynamic behavior [46,47].

7.12. Drug solubility: To check the solubility an excess amount of drug is added into the final formulation. After sonicating for15mins followed by continuous stirring up to 24 h at room temperature done and the nit should centrifuge (6000 rpm for 10 min). Then filter out and check the concentration of supernatant by the help of UV-spectrophotometer an calculate the amounts of soluble drugs [44].

7.13. In-vitro drug release: By the help of a modified Franz diffusion cell apparatus in-vitro drug release study is performed and calculate the drug content by using a UV spectrophotometer at specific wavelength [44].

8. Application Of Microemulsion System

8.1. Microemulsion In Pharmaceuticals- Microemulsions are promising pharmaceutical delivery systems due to their ease of formulation, stability, and high solubilization capacity. They effectively deliver both lipophilic and hydrophilic drugs, enabling controlled and sustained release across various administration routes (oral, topical, transdermal, ocular, and parenteral). Advantages include enhanced drug absorption, reduced toxicity, and minimized side effects. Applications span diverse drug types, including antineoplastics, peptides, steroids, anesthetics, anti-infectives, vitamins, and anti-inflammatory agents.

Microemulsions ensure biocompatibility, reduced immune reactions, and effective drug delivery, making them superior to traditional emulsions. Recent innovations include enzyme-based nanoparticles and microencapsulation for advanced therapeutic applications. [58-60].

Table 11: Various approaches to deliver drug through Microemulsion system

Route of administration	Various Approaches
Oral	Drugs having high molecular weight which may undergo enzymatic or biodegradation in the GIT can be given in the form of microemulsion, like the therapeutic peptides and proteins. The systemic uptake of peptide from microemulsion is dependent on different factors like particle size, type of lipid phase of microemulsion, digestibility etc. They conclude that microemulsion formulation improve the oral bioavailability of peptides for ex-cyclosporine [60]. • Kawakami and coauthors done a study to increase the oral bioavailability of a poorly soluble drug "Nitrendipine" by prepare a microemulsion formulation compared to a suspension or an oil solution, and they have concluded that the effect of fed state on the oral adsorption of nitrendipine became increases with the micro- emulsion formulation than its suspension formulation [61].
Topical	Microemulsions is a promising delivery system that gives sustained or controlled release of drug for percutaneous, peroral, topical, and transdermal, administration. Enhanced absorption of drugs, modulate the release kinetics of the drug and minimize the toxicity [62]. • Zao X et al studied micro-emulsion vehicle as a conceivable matrix for transdermal delivery of theophylline [69]. • Dalmore MEA and Oliveira AG done a study on the interaction of piroxicam with β-cyclodextrin, hexadecyl trimethyl ammonium bromide based microemulsion and ME in the presence of β-cyclodextrin, aimed at the optimization of topical drug delivery [63].

Occular	Eye is a very valuable organ of animals. Ophthalmic drug delivery is most challenging areas, facing the pharmaceutical scientist. The anatomy, physiology and biochemistry of the eye render this organ intricately in vulnnearable to foreign substances. The challenge faced by the formulator is to circumvent the protective barriers of the eye without causing sensitive eye tissue damages. The primitive ophthalmic solutions, suspensions and ointment dosage forms sometimes is not sufficient to combat some virulent diseases. However, due to their intrinsic properties and specific structure, the MEs are a promising dosage form for the natural defense of the eye. Indeed, because they are prepared through auto emulsification process, and easily sterilized, they are stable at any temperature and have a high drug dissolving capacity.[64]
Parenteral	Parenteral administration (particularly through involute) of poorlysolubledrugs is a major problem because low amount of drug actually delivered to a targeted site and can't predict the actual dose. Microemulsion formulations than macro emulsion systems are advantageous to delivered drug parenterally due to very small(micro-ranges) particle size and have a longer residence time in the body. Both O/W and W/O micro emulsion can be used for Parenteral delivery [65]. • Park KM and coauthors done study to improve the solubility of Flurbiprofen a poorly water-soluble drug, in an oil-in water (o/w) microemulsion that is suitable for parenteral administration [66]. • Lei H and coworkers prepared a Paclitaxel ME as an alternative for paclitaxel injection (Taxol) and the hypersensitivity evaluation and pharmacokinetic behavior in rats were conducted to assess the new ME [67].

Table 12: Marketed Products Available in Microemulsion form [68]

Drug name	Product name	Company	Dosage form	Uses
Amprenavir	Agene rase	GSK	Capsule (SGC)	Antiretroviral
Ritonavir	Norvig	AbbVie, NC	Liquid	Antiretroviral
Tipranavir	Aptiva's	Boehringer Ingelheim	Capsule (SGC)	Antiretroviral
Cyclosporin	Neural	Novartis	SMEDDS	Immunosuppressant

8.8. Analytical Applications of Microemulsions: Applications of micro-emulsions are enormous in the area of analysis, viz. chromatography, laser-excited photo ionization spectroscopy, etc. Hydrophobicity characteristics of solute through micro-emulsion electro kinetic chromatography (MEEKC) has been endeavored [94], which make available a rapid and reproducible method to get hydrophobic parameters of solvents. As solubilized media, spectroscopic shift reagents, peak intensity amplification agents, etc. micro-emulsions are able to progress the function of analytical spectroscopic techniques. Micro-emulsion system is very useful as a media in analytical spectroscopy and in analytical sensitivities. Various studies have been testified to determine the quantity of zinc, aluminum, copper, cadmium, manganese ions using micro-emulsion as well as mixed micro-emulsion-based systems [68, 69].

8.9. Microemulsions in Agrochemical Industry: In agrochemical industry micro-emulsions system have variety of applications, of which micro-emulsion-based pesticide systems are very popular. To minimize the excessive use of agrochemicals, increased the efficacy of pesticides is very vital aspect, 'micro-colloidal aqueous emulsion is used widely to overcome such problem. Phenoxy herbicides, an organic water insoluble compounds shows better effectiveness when formulate into a O/W micro-emulsion than normal emulsions to normalize the growth of plant. Micro-emulsions formulated with a hydro tope have more solubility capacity of many herbicides. W/O micro-emulsions is most effective to hold mineral such as copper, iron and beneficial for mineral-deficient crops. Oil phase of the micro-emulsion systems is able to hold various trace element on the leaves even during wet conditions, till the trace element is being adsorbed [70].

Table 14: Some Reports on drug loaded Microemulsion for improvement of their Pharmacokinetics [71]

Drug name	Route	Purpose/Results
Flurbiprofen	Parenteral	Increased the solubility
Apormorphie-Hcl	Transdermal	Increased the permeability
Ketoprofen	Transdermal	Enhancement of permeability
Prilocainne-Hcl	Transdermal	Increased the solubility
Estradiol	Transdermal	Improvement the solubilization
Aceclofenac	Dermatological	Increased the solubility

9.CONCLUSION

Microemulsions currently play a significant role as drug delivery systems in both research and industrial applications. They provide an effective environment to address the challenges of poor water solubility in highly lipophilic drug compounds, ensuring more reliable and reproducible bioavailability. Additionally, microemulsions are beneficial for optimizing drug targeting without systemic absorption. Despite their advantages, there are challenges related to the gastrointestinal tract (GIT) barriers that must be overcome for microemulsion formulations to reach target cells. Microemulsions possess the capability to protect labile drug substances, control drug release, and reduce patient inconsistency. Furthermore, they have been demonstrated to be suitable for most routes of administration, and are now recognized globally as a promising novel drug delivery system.

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