IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
August 2023 Vol.:28, Issue:1

Review on Self Micro-Emulsifying Drug Delivery System

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

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Submitted: 25 July 2023
Accepted: 18 August 2023
Published: 30 August 2023

Keywords: oral route, self-micro emulsifying, surfactant, bioavailability, absorption, ternary phase diagram.

ABSTRACT

In many diseases, the oral route has always been the favored route of pharmaceutical delivery, and it is still the first approach explored in the development of new dosage forms today. The main problem with oral pharmaceutical formulations is low and variable bioavailability, which is caused by poor water solubility and consequently implies formulation difficulties. More than 40% of potential therapeutic candidates have limited water solubility. Many approaches have been taken to address these concerns, including altering the solubility of the medicine or keeping it liquid during the gastrointestinal transit time. Emulsion pre-concentrates, lipid solutions, and emulsions have gotten a lot of interest since they can be turned into physically stable formulations that are suitable for encapsulating such poorly soluble medications. Self-micro has recently gained popularity. More emphasis has been placed on emulsifying drug delivery systems (SMEDDS). This is primarily because these systems are physically stable, easy to manufacture, and can be filled in soft gelatin capsules. Once in the gastrointestinal tract, these systems will produce a drug-containing micro-emulsion with a huge surface area. The self-micro emulsifying drug delivery framework is one method for enhancing the solubility of hydrophobic drugs. This technology can be used to manufacture medication that is insoluble in water by solubilizing it in the lipid vehicle and allowing it to absorb through the membrane. Lipids and surfactants are utilized to improve medicine solubility and absorption. This enhances the drug's solubility and consequently its rate of dissolution. This technique attracted attention because it improves medication bioavailability. This page provides a comprehensive assessment of SMEDDS for both current and future work.

1. INTRODUCTION:

Welcome to the comprehensive review on Self Micro Emulsifying Drug Delivery Systems (SMEDDS). In this article, we will delve into the intricacies of SMEDDS, a revolutionary approach in the field of pharmaceuticals.(1) With its potential to improve drug solubility, bioavailability, and therapeutic efficacy, SMEDDS has garnered significant attention from researchers and pharmaceutical companies alike. In this review, we will explore the underlying principles, benefits, and challenges associated with SMEDDS, and how it has the potential to revolutionize drug delivery systems.(2) So, let's begin our journey into the world of SMEDDS! Among the different drug administration methods, the oral route is thought to be the most practical and patient-favored. One of the major factors affecting a medicine's oral bioavailability is its solubility because a pharmacological ingredient must dissolve in the GI tract's aqueous environment before it can be absorbed.(3) Approximately 40% of all lipophilic medications are administered orally. Because of their poor water solubility, new chemical entities discovered during drug discovery programs (i.e. BCS Class II Drugs) present the biggest hurdle.4 the number of inferior water-soluble therapeutic candidate molecules has steadily increased because of current drug development strategies, and more than 50% of newly discovered chemical compounds with pharmacological activity have low water solubility and are lipophilic. bioavailability, and therapeutic efficacy, SMEDDS has garnered significant attention from researchers and pharmaceutical companies alike.(4,5)

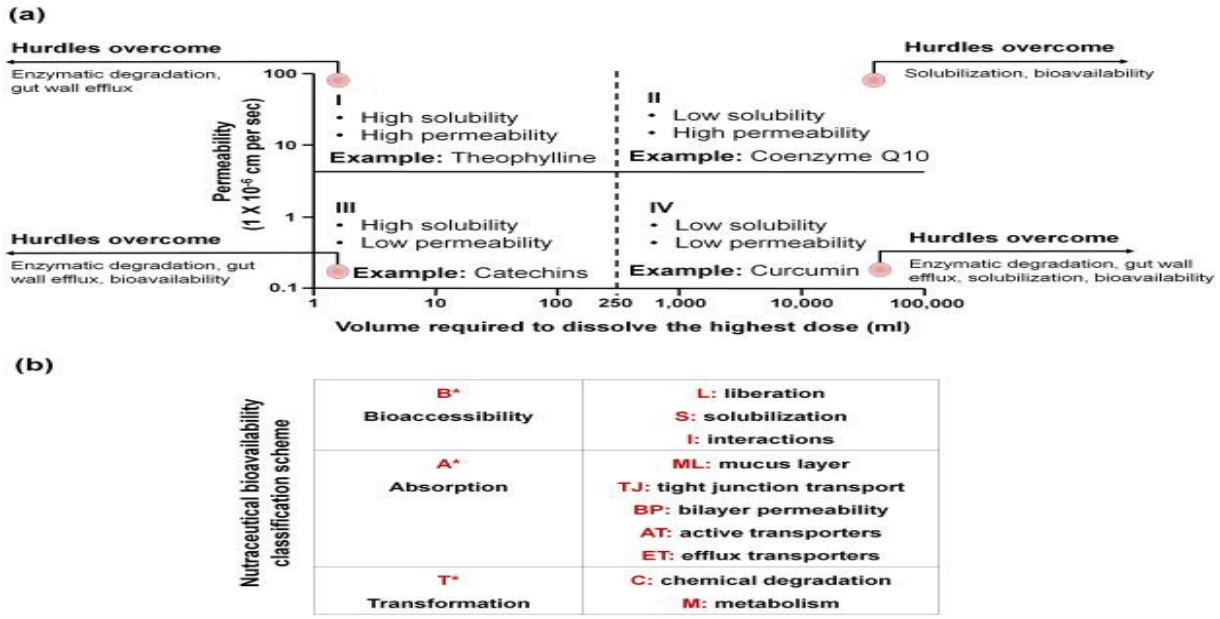
In this review, we will explore the underlying principles, benefits, and challenges associated with SMEDDS, and how it has the potential to revolutionize drug delivery systems. So, let's begin our journey into the world of SMEDDS! Among the different drug administration methods, the oral route is thought to be the most practical and patient-favored.(4,6) One of the major factors affecting a medicine's oral bioavailability is its solubility because a pharmacological ingredient must dissolve in the GI tract's aqueous environment before it can be absorbed.1 2 3 Approximately 40% of all lipophilic medications are administered orally.(5,7) Because of their poor water solubility, new chemical entities discovered during drug discovery programs (i.e. BCS Class II Drugs) present the biggest hurdle.4 The number of inferior water-soluble therapeutic candidate molecules has steadily increased because of current drug development strategies, and more than 50% of newly discovered chemical compounds with pharmacological activity have low water solubility and are lipophilic.(8,9)

Particle size reduction (micronation) is one method that has been thoroughly researched to increase the oral bioavailability of such medications. Salt generation, solubilization based on cosolvents, surfactants, or nanosizing), complexation with cyclodextrins, etc.(7,8)

The dissolving rate of a medicine can be increased by altering its physicochemical qualities, such as via salt production and particle size reduction, however these techniques are not always feasible, for instance, it is impossible to make salts of neutral chemicals. Additionally, weak acid and basic salts may revert to their original acid or base forms and cause aggregation in the digestive system. (2) Particle size reduction may cause static charges to accumulate, provide handling challenges, and is not always beneficial. favored in situations where very fine particles have inadequate wettability.(10) Other formulation options, including the use of cyclodextrins, nanoparticles, solid dispersions, and permeation enhancers, have been used in an effort to get around these restrictions. Indeed, these methods have worked in a few carefully chosen instances.(11)

Lipid-based formulations have attracted great deal of attention to improve the oral bioavailability of poorly water soluble drugs. In fact, the most favored approach is to incorporate lipophilic drugs into inert lipid vehicles such as oils, surfactant dispersions, micro emulsions, self-emulsifying formulations, self-micro emulsifying formulations, and liposomes.(10) This could lead to increased solubilization with concomitant modification of their pharmacokinetic profiles, leading to increase in therapeutic efficacy. Solutions, suspensions, solid dispersions, and self-micro emulsifying drug delivery systems (SMEDDS) are just a few of the formulations available in lipid-based formulations.[1](2) self-emulsifying formulations, which are isotropic combinations of natural or synthetic oils with lipophilic or hydrophilic surfactants and co-solvents, spontaneously emulsify to produce an oil-in-water emulsion or micro emulsion.(11)

SMEDDS are a type of emulsion that has drawn interest specifically because it can improve the oral bioavailability of medications that aren't well absorbed.(7) These systems are essentially co-surfactants that produce emulsions when mixed with water while requiring minimal energy input. Despite having potential pharmacodynamic efficacy, many drug candidates fail to reach the market due to poor water solubility.(6,8) additionally, to obtain the appropriate plasma level, weakly aqueous soluble drugs now on the market are delivered at substantially greater individual dosages than intended. Due to the toxicity issues caused by this, the advantages of therapy, patient comfort, and patient adherence.(4) (12)



(b)

Nutraceutical bioavailability classification scheme

B* Bioaccessibility	L: liberation S: solubilization I: interactions
A* Absorption	ML: mucus layer TJ: tight junction transport BP: bilayer permeability AT: active transporters ET: efflux transporters
T* Transformation	C: chemical degradation M: metabolism

figure no. 1

1.1.1 Advantages:

- SMEDDS can significantly improve the solubility of poorly water-soluble drugs, thereby increasing their bioavailability and therapeutic efficacy. (13)
- The microemulsion formulation allows for better drug absorption due to its ability to bypass the dissolution step, leading to faster and more consistent drug release. (14)
- SMEDDS can reduce the variability in drug absorption caused by food effects or other physiological factors, ensuring more predictable drug delivery. (13)
- By forming a stable microemulsion, SMEDDS can protect the drug from degradation and improve its shelf life. (13)
- SMEDDS offer the advantage of adjusting the drug dosage by simply changing the formulation's composition, making it easier to customize treatments for individual patients.(15)
- SMEDDS are more stable than emulsions due to their low energy consumption and the absence of certain steps in their manufacturing process. Crucial actions. SMEDDS can be created using only basic mixing tools, and preparation time is shorter than it is for emulsions.
- The formulation of SMEDDS allows for efficient absorption of poorly water-soluble medicines with dissolution rate-limited absorption, with stable time-profile of the plasma he

presentation of the poorly soluble drug in dissolved form, which skips the crucial phase in drug absorption known as dissolution, may be the cause of the drug's constant plasma levels.(16)

- The formulation of SMEDDS can protect drugs from being degraded in the GIT by chemical and enzymatic mechanisms because the medicine will be administered to the body as oil droplets.(16)

- Pre-concentrated microemulsion is preferable to microemulsion when dispensing in the form of liquid-filled soft gelatin capsules. SMEDDS are preferable to SEDDS because the former is less dependent on bile salts for the creation of droplets, which is believed to result in better medication absorption compared to SEDDS.(16)

1.1.2 Disadvantages:

- Designing SMEDDS requires expertise and can be challenging due to the need for a careful balance of surfactants, co-solvents, and oils to form a stable microemulsion. (17)

- Scaling up the production of SMEDDS may present difficulties and require specialized equipment.

- SMEDDS might not be suitable for all drugs, as some may not be compatible with the chosen excipients or interact adversely with the formulation components**.** (17)

- Despite improved bioavailability in most cases, certain drugs may still exhibit variable absorption with SMEDDS due to individual physiological differences.(17)

- In some cases, the use of SMEDDS may lead to gastrointestinal irritation or adverse effects, which could limit their application.(17)

1.2 Mechanism of self-emulsification:

Self-emulsification is a process in which a water insoluble substance, such as an oil, spontaneously disperses into tiny droplets in the presence of water form a stable emulsion. This phenomenon occurs without the need for external energy input or the use of traditional emulsifying agents like surfactants.(6)

1.2.1 The mechanism of self-emulsification typically involves the following steps:

A. Surfactant-like Behavior: The substance to be emulsified (e.g., oil) possesses surfactant-like properties due to its chemical structure. A surfactant a molecule with a hydrophilic (water-attracting) head and a hydrophobic (water-repellent) tail. In self-emulsification, the substance's molecular structure allows it to align at the oil-water interface, reducing the interfacial tension between the two phases.(16)

B. Formation of Nano-emulsion: When the water insoluble substance is introduced into water, the surfactant-like molecules arrange themselves at the oil-water interface, forming a protective layer around the oil droplets. This layer stabilizes the droplets and prevents them from coalescing.(17) **Spontaneous Dispersion:** Due to the surfactant-like behavior, the water-insoluble substance disperses spontaneously into small droplets when mixed with water. The energy required for this process comes from the thermal motion of the molecules and is sufficient to overcome the interfacial tension, leading to the breakup of the bulk oil into droplets. (18)

C. Formation of Stable Emulsion: The small droplets formed during self-emulsification are stabilized by the surfactant-like molecules that continue to cover their surfaces. This ensures the emulsion remains stable over time, preventing phase separation or coalesce of droplets.(18) Self-emulsification is commonly utilized in pharmaceuticals, cosmetics, and food industries to enhance the solubility and bioavailability of poorly water-soluble substances, such as certain drugs or essential oils. The process offers several advantages, including ease of preparation, improved absorption, and better product stability.(18) However, the success of self-emulsification depends on the specific properties of the substances involved, including their molecular structure and compatibility with water Self-emulsification occurs when the entropy trade that favors dispersion is bigger than the power necessary to increase the dispersion's floor location. Hence For emulsification to take place, the interfacial form must be free of resistance to surface shearing.(19) The addition of a binary aggregation (oil/non-ionic surfactant) to water creates the interface between the oil and aqueous non-stop phases. As a result of aqueous penetration across the interface, this is followed by solubilization in the oil part. This occurs until the solubilization limit at the interphase is reached. the dispersed liquid crystal (LC) will form as a result of aqueous penetration.(4) The unfastened strength of a typical emulsion is an immediate element of the

power required to build a new surface between the water and oil phases, and it can be used to produce a new surface between the water and oil stages.(6)

$$\delta G = \sum Ni\ \pi\ ri\ 2\ \sigma$$

Where:

δG is the free energy associated with the process (ignoring the free energy of mixing),

N is the number of droplets of radius r,

σ is interfacial energy with time

According to the aforementioned equation, the spontaneous creation of an interface between oil and aqueous phase is thermodynamically stable. elaborated on the spontaneous generation of emulsion, also known as self-emulsification, is measured in terms of the free energy necessary to produce the emulsion, which can be very low and positive or negative. Pouton proposed a link between the surfactant's emulsification properties and the system's phase inversion behavior.(20)

For example, if the temperature of an oil-in-water system stabilized by non-ionic surfactant(s) is raised, the cloud point of the surfactant is reached, followed by phase inversion. Because the surfactant is highly mobile at the phase inversion temperature, the o/w interfacial energy is minimized, resulting in less energy required for emulsification.(8)

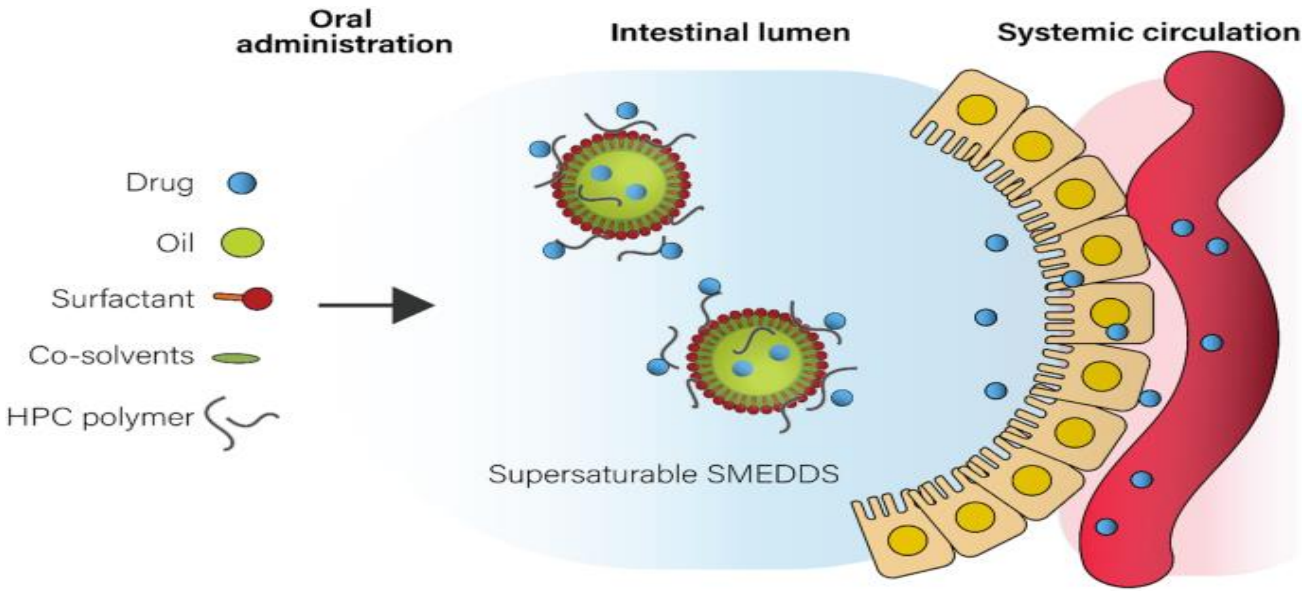


Figure no 2

1.3 Composition of SMEDDS:

The self- emulsification process is said to be particular to the nature of the oil surfactant pair.

The process is based on

1. Oils.

2. The concentration of surfactants and the oil/surfactant ratio.

3. The temperature at which self-emulsion takes place.

1.3.1 Oils:

The oil is one of the most significant excipients in the SMEDDS formulation, not only because it can solubilize the appropriate amount of the lipophilic medication, but also because it is a natural lubricant.(21) It can increase the fraction of lipophilic medication delivered by the intestinal lymphatic system, hence enhancing absorption from the GI tract depending on the molecular composition of the triglyceride. Long and medium chain triglyceride (LCT and MCT) oils with varying degrees of saturation were employed to create self-emulsifying compositions.(21) Furthermore, due to their low ability to dissolve large amounts of lipophilic medicines, edible oils, which may be the obvious and preferred lipid excipient choice for the development of SMEDDS, are not usually used.(22)

Vegetable oils that have been modified or hydrolyzed have been widely employed as excipients because they create good emulsification systems with a wide range of surfactants. Authorized for oral administration and display superior drug solubility qualities. They provide formulative and physiological benefits, and their breakdown products are similar to the natural end products of intestine digestion.(3) Novel semisynthetic medium chain derivatives, described as amphiphilic chemicals with surfactant characteristics, are gradually and efficiently replacing traditional medium chain triglyceride oils in the SMEDDS The oil grouping found in SMEDDS is approximately 40-80% altered and hydrolyzed vegetable oils, which have higher solubility and stability. excellent self-emulsifying ability.(2) Edible oils are not frequently used due to their inability to break down many lipophilic medicines. Altered or hydrolyzed vegetable oils have been widely used as excipients for good emulsification frameworks with a large number of surfactants recommended for oral organization and demonstrate enhanced medicine dissolvability features.(11)

1.3.2 Surfactant:

A variety of surfactant-containing mixtures could be used in the design of self-emulsifying frameworks, but because not all surfactants are suitable for ingestion, the decision is limited. Nonionic surfactants with a relatively high hydrophilic lipophilic equalization (HLB) are the most widely suggested.(23) When selecting a surfactant, safety is an important consideration. Surfactants have a limited ability to self-emulsify. Non-ionic surfactants are less toxic than ionic surfactants, although they may cause reversible changes in the environment(24). The gut lumen's permeability. Surfactant concentrations in the range of 30% to 60% w/w are often used to shape stable SMEDDS. It is critical to choose the surfactant concentration carefully because several surfactants might cause GI irritation. (25)

The four major groups of surfactants are defined as follows:

Anionic Surfactants: the hydrophilic group carries a negative charge, such as carboxyl (RCOO-), sulphate (RO-SO3-), or sulphonate (RSO3-).

Potassium laurate and sodium lauryl sulphate are two models.

Cationic surfactants: the hydrophilic gathering place carries a positive energy. quaternary model Ammonium halide is a chemical compound.

Ampholytic surfactants: (also known as zwitterionic surfactants) possess both a negative and positive charge. A charge that is positive. Sulfobetaines are the model.

Non-ionic surfactants: Where the hydrophilic collection takes place conveys no fee but implies water solvency from unusually polar groups, for example hydroxyl (OCH2CH2O) or polyoxyethylene (OCH2CH2O). Models: Polysorbates (Tweens), Sorbitan Ester.

Because single alkyl chains are more penetrative, bulky surfactants like polysorbates and triglyceride ethoxylates are less hazardous.(24–26) Typically, To generate stable SMEDDS, surfactant concentrations vary between 30 and 60% of the entire formulation. It is critical to accurately estimate the surfactant concentration because excessive amounts of surfactant might induce GI irritation. (12,27)The extremely small lipid droplet size produced by SMEDDS formulations, on the other hand, facilitates quick stomach emptying and extensive dispersion throughout the GIT, minimizing exposure to high local surfactant concentrations and thereby lowering irritation risk.(23)

1.3.3 Co-surfactants/Co-solvents:

Usually, the formulation of a successful SMEDDS requires high concentrations of surfactant (up to 50%) and addition of co-surfactants aids in self-emulsification. Generally, co-surfactant of HLB value 10-14 is used with surfactant to decrease the oil-water interfacial tension, fluidize the hydrocarbon region of interfacial film, increase the drug loading to SMEDDS and allows the spontaneous formation of microemulsion.(11,23) Hence, surfactants (hydrophilic or lipophilic) and/or amphiphilic solubilizers are used for this purpose. (2,24) The addition of the co-emulsifiers or solubilizers in SMEDDS may result in an expanding self-micro-emulsification region in the phase diagrams.

The construction of an optimal SMEDDS necessitates somewhat high surfactant fixations (often greater than 30% w/w), yet this induces GI aggravation. As a result, co surfactant is used. Surfactant convergence is reduced.(12) The co-surfactant's and surfactant's job is to reduce interfacial strain to a minor, even temporary, negative value.(24) At this point, the interface would stretch to form fine distributed beads, adsorbing more surfactant and surfactant/co-surfactant until their mass condition is sufficiently depleted to make interfacial strain positive again.

The method termed as’ unconstrained emulsification' frames the micro emulsions. Natural solvents suitable for oral organization include ethanol, propylene glycol (PG), and water. Polyethylene glycol (PEG), for example, can aid in the dissolution of a large amount of either the hydrophilic surfactant or the medication in the lipid base and can operate as a co-surfactant in oneself emulsifying drug conveyance systems.(27)

Organic solvents suitable for oral organization (ethanol, propylene glycol (PG), polyethylene glycol (PEG), and so on serve as co-solvents. may help with the dissolution of a significant amount of either the hydrophilic surfactant or the medication in the lipid base and can act as a co-surfactant in self-emulsifying drug conveyance frameworks, despite the fact that alcohol free self-emulsifying microemulsions have also been depicted in the writing. (1) When combined in case dose structures, such frameworks may exhibit a few focal points over previous definitions, because alcohol and other unpredictable co-solvents in ordinary self-emulsifying details are known to relocate into the shells of delicate gelatin or hard fixed gelatin containers, causing the precipitation of the lipophilic medication. (13,28)

1.3.4 Active Agent:

When low solubility is the primary cause of limited medication absorption, lipid-based formulations are generally preferable SMEDDS can achieve maximum bioavailability at very low dosages, especially for medicines with a high octanol: water partition coefficient. (29) The drug's absorption from SMEDDS is mostly determined by its solubility in water and lipid phase.

Compounds with low bioavailability due to pre-systemic metabolism can be synthesized as SMEDDS if they have a high solubility in long-chain triglycerides (> 50 mg/ml) octanol: water partition coefficient of greater than five Excipients utilized in various preparations are depicted.(30)

1.4 DRUG PROPERTIES APPROPRIETES FOR SMEDDS

Medication should be oil dissolvable and the portion dose should be reduced.

A high melting point medication is unsuitable for SMEDDS.

The Log P value should not be too high

Solvency: The drug should be water insoluble. Log P should be more than 4 (lipophilic), with high dissolvability in LCT for lymphatic absorption (>50mg/ml). 19 BCS classes II and IV.

Low dose: To increase medicine bioavailability and reduce molecule size, the amount should be low, preferably 40mg.

Poor BA: The bioavailability should be low in order to improve the medication's dissolvability.

Low melting point: For optimal medicine absorption, the melting point should be low.

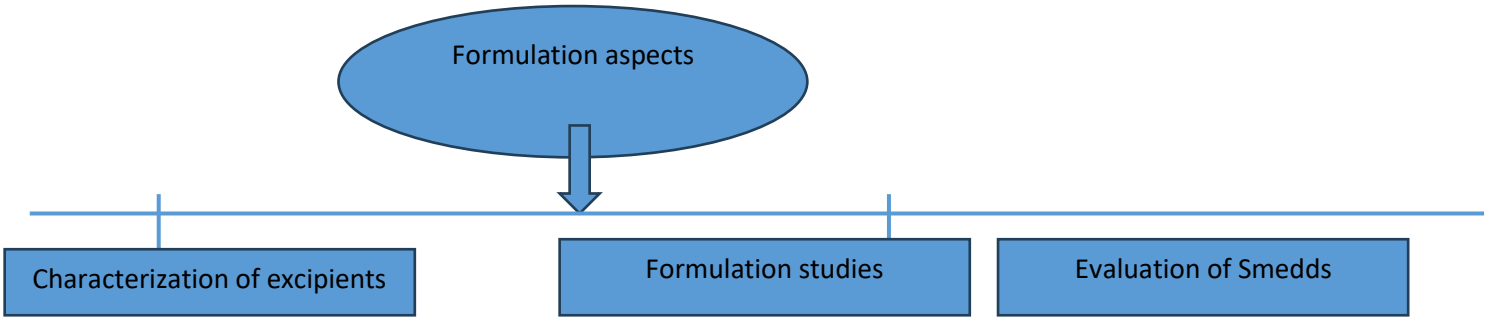
Chemical and physical stability is required.

1.5 SMEDDS FORMULATION:

Lipophilic medications can be delivered in a variety of ways, including microemulsions, lipid solutions, and lipid suspensions. emulsion, dry emulsion, whose formulation involves a large number of possible excipient combinations; additionally, to understand these lipid-based formulations and to get a clear picture of all these different systems, a specific classification

system known as the 'lipid formulation classification system' has been introduced.(31,32) The classification aids in better understanding the destiny of various lipid formulations in vivo. Lipid-based formulations are categorized into four classes depending on their composition and the effect of dilution and digestion on their capacity to avoid drug precipitation.

Hydrophobic drugs dissolve more easily in synthetic hydrophilic oils and surfactants than in typical vegetable oils. Similarly, ethanol, PG, and PEG contribute to improved drug dissolvability in lipid vehicles.(13,33)



The following points should be considered when developing a SMEDDS -

1.5.1 Determine the medication's solubility in various oils, surfactants, and surfactants.

Determine dissolvability by placing an excessive amount of drug in small vials containing 2 ml of selected oil, surfactant, and surfactant separately. The drug was mixed with a glass rod for 30 minutes before the vials were preserved for sonication for about 2 hours. The vials are tightly sealed and regularly combined for 72 hours in an orbital shaking incubator at 250 ^{0}C.The mixture was then centrifuged at 3500 rpm for 20 minutes. The mixture was then centrifuged at 3500 rpm for 20 minutes. After suitable dilution with methanol or alcohol, 1ml supernatants are separated and broken down in methanol or alcohol, and dissolvability is measured by UV-spectrophotometer at specified frequency. In any event, the arrangements are unsatisfactory after dilution. So oils should be diluted with 66% v/v chloroform in

methanol and surfactants with 7% v/v chloroform in methanol Choose an oil, surfactant, and co-surfactant based on the drug's dissolvability.(13)

Determine the surfactant-to-co-surfactant ratio: The emulsifying effect is acceptable if the surfactant to co-surfactant ratio is more than 1:2.5 however the stability qualities are poor at this ratio. Fixing the surfactant/co-surfactant balance to 1:1 is a good idea.(12)

1.5.2 Choosing surfactants and co-surfactants and evaluating their ability to self-emulsify

Surfactants' capacity to emulsify can be determined by homogenizing the mixture of the chosen oil and surfactant in an equal ratio. The ease of emulsification is determined by counting the piston revolutions needed to create a homogeneous emulsion after this mixture is put to double-distilled water.(26) Low piston inversions should be used and the resulting microemulsion should be evaluated for clarity, turbidity, and % permeability. Co-surfactants should also be screened using the same method, which involves combining the chosen surfactant with the oil phase and the co-surfactant.(25)

1.5.3 Phase diagram preparation:

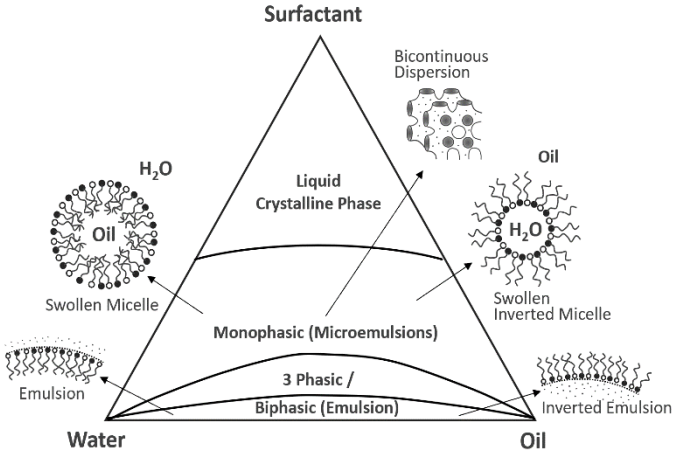
The phase behavior of three components, namely oil, water, and surfactant, is studied using the ternary phase diagram, however in the case of the most typical additional component in SMEDDS is the addition of a co-surfactant or solvent.(11,23) Three corners of the ternary diagram are 100% corresponding to each component. The ternary diagram can be referred to as a pseudo-ternary phase diagram if the fourth component is introduced since one of the corners represents the mixing of two components, such as surfactant and surfactant. (2,25)

The emulsification efficiency of mixes with various proportions of microemulsion components must be assessed in order to generate the pseudo-ternary phase diagram. Different compositions can result in the formation of various structures, including emulsions, microemulsions, micelles, inverted micelle forms, etc. By creating a phase diagram, it is possible to determine how these structures are formed.(34) This phase diagram provides information on the various compositions that create transparent single-phase solutions as well as the formulation's dilution capacity.

By maintaining a consistent ratio between two of the four components, pseudo-ternary graphs can be created. Three of the phase diagram's corners are typically formed by this ratio and the

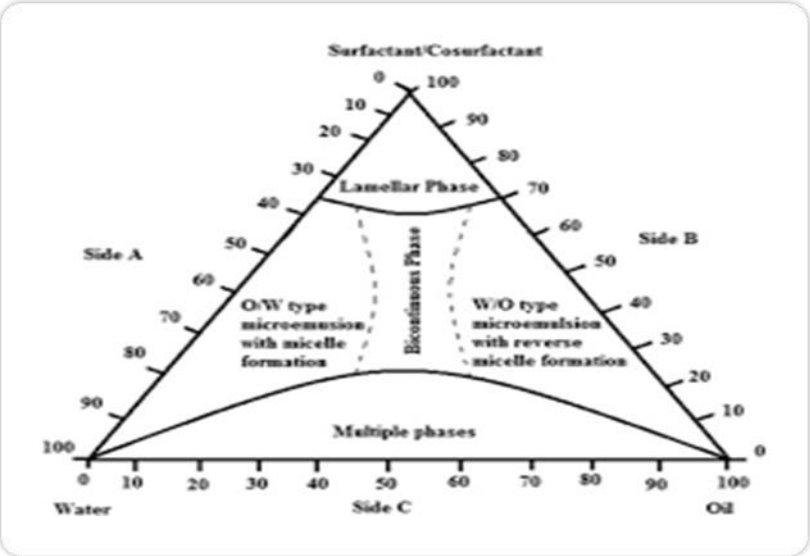
other two components.(21) Surfactant and co-surfactant are typically combined to create this set ratio (mixture), though oil and surfactant can also be included on occasion. The other component, which is typically water, is added in small amounts after this is combined with the necessary volume of the third phase as an oil or co-surfactant. (8) Prior to adding the fourth component, the solution is tested for clarity, flowability, self-emulsification time, and dispersibility. Each mixture's overall component percentage concentration should be 100%. Then, the pseudo-ternary diagram needs to be created using suitable software The relevant symbols in the phase diagram are to be used to identify samples that form a clear solution.(35) the region where When these sites are joined, the monophasic microemulsion's existing region is visible, and the vast area exhibits good emulsification efficiency.(18)

The phase conduct of each SMEDDS is emphasized. Carefully by utilizing the phase graph. One of the most important features of SMEDDS is the ability to display progressions when the framework is diluted, which may result in medication precipitation.(18) As a result, the phase behaviors of each SMEEDS should be meticulously investigated. Dissolvability was discovered by the ternary charts were devised to tranquillize in different surfactant \ surfactant amount.



STEP A: -Solubilizing an insufficiently water-soluble drug and additionally a pharmaceutical ingredient in a mixture of surfactant, co-surfactant, and co-surfactant. surfactant solvent.(36,37) Now, mix the oil stage that has been properly prepared, if necessary, by warming or other preceding procedures, to the solubilized drug formulation and thoroughly blended.(38,39)

STEP B: - The emulsion might then be added to a suitable dosage form, such as a soft or hard-filled gelatin capsule, and allowed to settle Oil, Surfactant, Co-surfactant & Drug.



1.5.4 SMEDDS preparation

Involves vertexing once the medication has been added to the oil, surfactant, and co-surfactant combination. In a few if the excipients are introduced to the drug solution after the drug dissolves in one of the excipients. (40) The solution must then be thoroughly included before being checked for cloudiness. The solution should, if necessary, be boiled to a clear solution after equilibrating for 48 hours at room temperature. The mixture needs to be kept in capsules with the right volume.(41)

1.5.5 Method of Preparation:

1.5.5.1 Phase Titration Method: Microemulsions are created utilizing spontaneous emulsification as the preparation method. A phase diagram can be useful for understanding the intricate web of interactions that can develop when several components are combined. based on the chemical makeup and concentration of each component, formed together with a variety of association structures (including emulsion, micelles, laminar, hexagonal, cubic, and different gel and oil dispersions).(41,42) It is crucial to comprehend the phase equilibrium and identify the phase limits because each corner of the figure represents 100% of the component under consideration. Considering the composition, that is, whether it is rich in oil or not, the region can be split into w/o or o/w microemulsion. To rule out metastable systems, careful monitoring is required. (43,44)

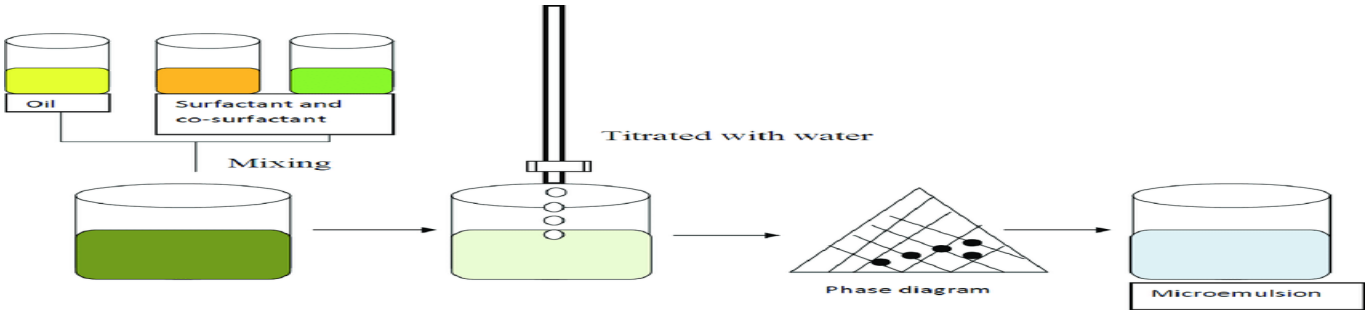


Fig no. 3

1.5.5.2 Phase Inversion Method:

Adding too much of the dispersed phase or reacting to it are two ways that microemulsions might undergo phase inversion. the degree of heat During phase inversion, there are significant physical changes that take place, including changes in particle size that can have an impact on drug release in vivo and in vitro.(17,45) These techniques work by altering the surfactant's natural curvature. By altering the system's temperature, which induces a transition from a low-temperature O / W micro-emulsion to a W / O micro-emulsion at higher temperatures (transition phase inversion), this can be accomplished in the case of non-ionic surfactants. (16,46) As the system cools, it passes through a point with little surface tension and little spontaneous curvature, which promotes the creation of finely divided oil droplets.

As the system cools, it passes through a point with little surface and no spontaneous curvature tension, which promotes the production of tiny oil droplets.(16) The phase inversion temperature (PIT) process is what is involved in this procedure.

Other factors, such as salt content or pH value, can be considered in addition to temperature instead of being the only one. Changing the volume proportion of water is another way to transition the spontaneous radius of curvature.(15,47) The formation of water droplets in an initially continuous oil phase is accomplished by progressively introducing water to the oil. When the volume proportion of water increases, the spontaneous curvature of the water/oil microemulsion's surfactant, which initially stabilizes the mixture at the point the inversion. (13,32)At the o/w interface, flexible monolayers formed by short-chain surfactants result in a discontinuous micro-emulsion at the site of inversion.(31)

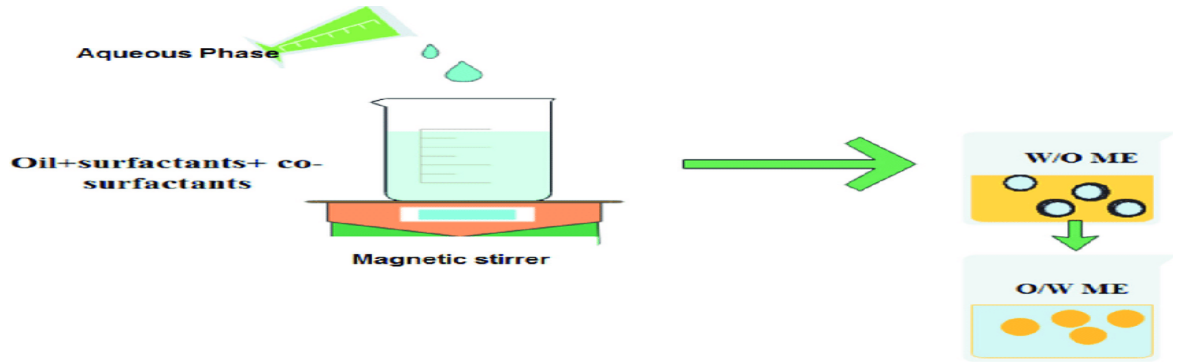


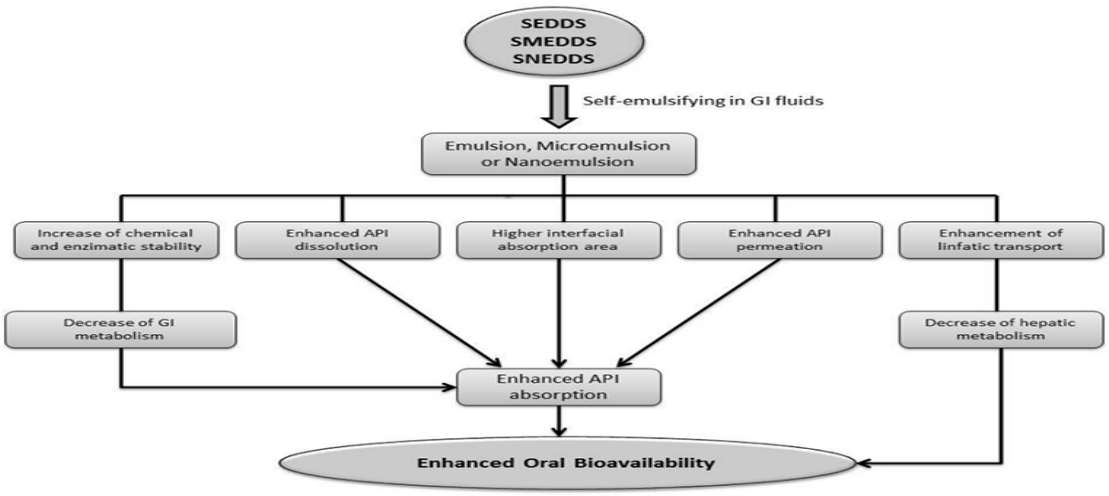
Fig no .4

1.6 BIOPHARMACEUTICAL ASPECTS OF SMEDDS

These systems increase absorption from the gastrointestinal tract by accelerating the dissolution process, facilitating the formation of solubilized phases through particle size reduction to the molecular level, yielding a solid-state solution within the carrier, altering drug uptake, efflux, and disposition by altering enterocyte-based transport60, and enhancing drug transport to the systemic circulation via the intestinal lymphatic system.(28)

1.6.1 Effect of Lipids

Because of the multiple methods through which lipids can change the bioavailability of orally delivered medications, the effect of lipids on bioavailability is exceedingly complex. The drug's biopharmaceutical properties. Factors such as triglyceride acid chain length, saturation degree, and lipid amount supplied can all have an impact on medication absorption and blood/lymph distribution.(48)



1.6.1.1 Effect on rate of gastric emptying:

An increase in stomach residence time indicates that the medicine is being delivered to its site of action. The lipid component of meals, in particular, has an important influence in the absorption of lipophilic medicines. Lipids in the GI tract cause a delay in gastric emptying, resulting in prolonged gastric transit time and increased oral bioavailability of the co-administered lipophilic medication. (15)

This is explained by a high fat meal's propensity to activate biliary and pancreatic secretions, decrease metabolism and efflux activity, enhance intestinal wall permeability, and extend GIT residence duration and transfer via lymphatic system.(14) Triglycerides and long chain fatty acids are important in extending GIT residence duration.

1.6.1.2 Effect on Drug Digestion and Solubilization

The rate and extent of absorption of a medicine are determined by the balance between its solubility in the aqueous environment of the gastrointestinal lumen and its penetration across the lipophilic membrane of enterocytes. Following SMEDDS consumption, gastric lipase begins the digestion of exogenous food TG and formulation TG(46). Simultaneously, mechanical mixing in the stomach (propulsion, grinding, and retropulsion) promotes the creation of a crude emulsion (composed of aqueous gastric fluid and lipid digestion products).

Pancreatic lipase, together with its cofactor co-lipase203, completes the breakdown of TG to diglyceride, monoglyceride, and fatty acid in the small intestine. Pancreatic lipase produces 2-monoglyceride and free fatty acid predominantly at the sn-1 and sn-3 sites of TG69. The small intestine also undergoes chemical digestion of formulation- or biliary-derived phospholipid (PL), with pancreatic phospholipase A2 hydrolyzing a single fatty-acid molecule from the sn-2 position of PL to generate lysophosphatidylcholine and fatty acid The presence of exogenous lipids in the small intestine induces the release of endogenous biliary lipids from the gallbladder, such as bile salt (BS), PL, and cholesterol.(16,17)

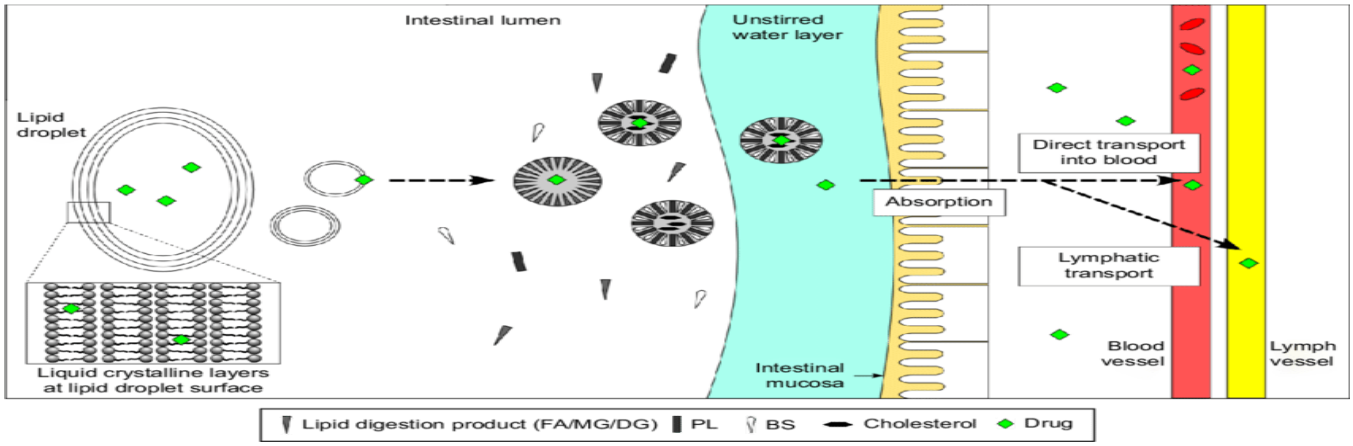


Fig no 5

1.6.1.3 Enhancement of intestinal lymphatic transport

Lipids may boost the amount of lymphatic transport and increase bioavailability directly or indirectly by reducing first pass metabolism in highly lipophilic medicines 62-64. Lipids enhance the amount of TG-rich lipoproteins in the blood, which react with medication molecules.

Lipoprotein-drug complexes improve intestinal lymphatic transport, causing changes in drug disposition and, ultimately, changing the kinetics of poorly soluble medicines' pharmacological activities.(45,49)

The effect of structured triglycerides with varied intra molecular structures and chain lengths inserted into a SMEDDS on intestinal lymphatic transport and halofantrine absorption into the blood was studied The SMEDDS formulation contained 29% w/w LLL, LML, or MLM structured triglyceride (L: long chain fatty acid, C18; M: medium chain fatty acid, C8-10).(43) The droplet size of the MLM and LML micro-emulsions was 50 nm. The lymphatic transfer of halofantrine after 12 hours, given as the cumulative percentage of the administered dose (mean% dose S.E.) was 27.4 1.3 in the LML and 17.9 1.3 in the MLM. (42)

The findings suggested that the structural development of the triglyceride triggered a significant level of lymphatic movement. As a result, it was hypothesized that medium chain fatty acids improved absorption into the systemic blood circulation whereas long chain fatty acids improved lymphatic transport.(50) To improve the oral bioavailability of highly lipophilic medicines, the absorption profile of a medication packaged into a SMEDDS could

be altered by altering the medium and long chain triglyceride content in the formulation.(51) (40)

1.6.1.4 The influence on intestinal permeability

The oil component changes the drug's solubility in SMEDDS by permeating the hydrophobic region of the surfactant monolayer. Oil penetration varies according to the molecular volume, polarity, size, and shape of the oil molecule. Drug solubility in SMEDDS is always greater than drug solubility in separate excipients that combine to generate SMEDDS.(43) However, such increased solubility is heavily dependent on the drug's solubility in the oil phase, the drug's interfacial location, and drug-surfactant interactions at the interface. Light scattering investigations revealed that oils with low molecular volume behave like co-surfactants and penetrate the surfactant monolayer. This results in thinner polyoxyethylene chains around the micelle's hydrophobic core, interrupting the major locus of drug solubilization and preventing increased drug solubility. (52)

Large molecular volume oils, on the other hand, form a distinct core and do not penetrate the surfactant effectively monolayer. The microstructure and solubility of the drug in the excipients were discovered to affect the locus of drug solubilization. For phytosterols, the locus of drug solubilization was discovered to be at the micelle interface, but for cholesterol, it was discovered to be between the hydrophobic head groups of surfactant molecules.(53) This is owing to the changed side chain flexibility of phytosterol as a result of the extra substitution of the alkyl side chain compared to cholesterol.

1.6.1.5 Metabolism and efflux activity are reduced.

Excipients in SMEDDS have been demonstrated in some cases to block both pre-systemic drug metabolism and intestinal efflux mediated by P-gp, resulting in enhanced oral absorption of cytotoxic medicines. (54)Certain lipids and surfactants have been shown to lower the activity of intestinal efflux transporters, as shown by the p-glycoprotein efflux pump, as well as the extent of enterocyte-based metabolism. As a result of the decrease in P-gp drug efflux, absorption of lipophilic medicines packaged as SMEDDS from the GI tract may be enhanced. In addition to a multidrug efflux pump, the intestinal phase I metabolism the role of cytochrome P450s in oral medication bioavailability is gradually becoming recognized.(20)

1.6.2 Effect of surfactants

1.6.2.1 Effect of permeability

Surfactants increase permeability by interfering with the lipid bilayer of the single layer of the epithelial cell membrane 81, which together with the unstirred aqueous layer forms the rate-limiting barrier to drug absorption/diffusion62. As a result, most drugs are absorbed via the passive trans-cellular route Impact on Droplet Size.(8)

SMEDDS is formed in lipid mixtures with greater surfactant and co-surfactant/oil ratios. The concentration of surfactant necessary to generate a stable SMEDDS ranges from 30 to 60% (m/m) 86. To avoid gastrointestinal irritation, the lowest feasible surfactant concentration should be employed. SMEDDS's extremely small droplet size facilitates quick stomach emptying and low local concentrations of the surfactant, decreasing gastric discomfort. (7)The size of the droplets and the concentration of the surfactant utilized have a relationship. Surfactant concentration has been demonstrated to have varied impacts on emulsion droplet size. An increase in surfactant concentration leads to a decrease in droplet size due to the stabilization of surfactant molecules at the oil-water interface, while the opposite is conceivable due to increased water penetration into oil droplets, which leads to their breakdown. (22)

Increasing the surfactant concentration may result in droplets with lower mean droplet size in some situations, such as in the case of a mixture of saturated C8-C10 polyglycolide glycerides (Labrafac CM-10). This could be explained by the stabilization of the oil droplets as a result of surfactant molecules localization at the oil-water interface.(2,3) On the other hand, increasing surfactant concentrations may cause the mean droplet size to rise in some circumstances. The phenomenon could be related to interfacial disruption caused by greater water penetration into oil droplets mediated by increased surfactant concentration, resulting in oil droplet ejection into the aqueous phase. Surfactants' role in SMEDDS is to reduce interfacial tension and adjust the spontaneous curvature of the interface, allowing dispersion and providing a flexible film that can easily cover the lipid core of the emulsion droplets, resulting in the spontaneous formation of a nano- or micro-emulsion. (23)Increasing surfactant activity at the water-oil contact results in a decrease in interfacial tension. Furthermore, the addition of a second surfactant to the system would typically result in a further fall in interfacial tension to a very small, even transiently negative value, at which the interface would expand to produce finely dispersed droplets.(24)

1.7 Characterization of SMEDDS

1.7.1 Visual Evaluation: A visual evaluation can be used to gauge self-emulsification. Once diluted an opaque and milky-white appearance of SMEDDS with water denotes the creation of a microemulsion. A transparent, isotropic, clear solution, on the other hand, denotes the creation of a micro-emulsion.(24,25) By visual inspection, the drug may also precipitate in diluted SMEDDS. Formulations are deemed stable if there is no sign of drug precipitation. When the formulation comprises water-soluble co-solvents, precipitation is frequently experienced and can be avoided by raising the surfactant content.(25)

1.7.2 Thermodynamic stability: A lipid-based formulation's physical stability is also essential to its performance and can be negatively impacted by the medication precipitating in the excipient matrix. Additionally, inadequate formulation physical stability might cause the excipient to phase separate, affecting not only formulation. Performance, but also one's outward look. Brittleness or deformation might also result from formulation and gelatin capsule shell incompatibility. delayed breakdown or insufficient drug release.(12)

1.7.3 Heating Cooling Cycle: Six cycles between 4°C and 45°C, with storage at each temperature for at least 48 hours, are investigated. Centrifugation testing is done on formulations that remain stable at these temperatures.(27)

1.7.4 Centrifugation: Formulations that have passed are centrifuged three times, once at 3500 rpm for 30 minutes and once at 210 ^{0C} and once at +25 ^{0}C, with storage at each temperature for at least 48 hours. The freeze-thaw stress test is performed on those formulations that do not exhibit any phase separation.(48)

1.7.5 Freeze Thaw cycle: In the formulations that passed this test, there was no phase separation, creaming, or cracking.(28)

1.7.6 Analysis of Droplet Size: The kind and concentration of the surfactant have a significant impact on the size of the droplet. A microemulsion developed. Produces droplets with a very narrow size and size distribution for effective drug release, in vivo absorption, and stability. on dilution with water.(32) Spectroscopic methods, such as photon correlation spectroscopy, and microscopic methods are employed for droplet size analysis. For droplet size analysis, dynamic light scattering methods with the zeta meter can also be used. Before determining size, samples must be properly diluted. The polydispersity index (PDI) measurement gives useful data on the size distribution.(33)

1.7.7 Zeta Potential Measurement: A zeta potential analyzer or a zeta meter system is typically used to measure the zeta potential. The After adequate dilution, the emulsion's stability is indicated by the zeta potential value. Good formulation stability is indicated by a greater zeta potential. Due to the presence of free fatty acids, the zeta potential value is typically negative; however, when cationic lipids, such as oleyl-amine, are utilized, the positive charge develops. (13)Droplets with a positive charge has the ability to effectively interact with the GIT's mucosal surface. Strong electrostatic interactions characterize these interactions. Expect greater absorption along with adhesion.

1.7.8 Time for Emulsification:

Using a USP Type II dissolution device, add the formulation drop wise to the water-containing basket, and observe the formation of a clear solution with stirring while agitation is provided by a paddle at 50 rpm. This method can be used to determine the time needed for self-emulsion for the various formulations. Self-emulsification aids in evaluating the formulation's self-emulsification effectiveness. It was discovered that the kind of oil phase and the oil/surfactant ratio affect the rate of emulsification. Due to the quick ejection of oil droplets by water at the interface, a higher surfactant concentration results in a faster rate of emulsification. After the formulation has been dissolved in 0.1 N HCl while being shaken at body temperature, the emulsification time can also be determined visually.

1.7.9 Dispersibility test: Using a typical USP XXII dissolution equipment 2, the effectiveness is evaluated. 500 mL of water at a temperature of 37 ^{0}C 0.5 received one mL of each composition. A 50-rpm standard stainless steel dissolving paddle offered light agitation. The following grading system21 is used to visually evaluate the formulations' in vitro performance:

Grade A: A nano emulsion that forms quickly (within 1 minute) and is clear or bluish in color.

Grade B: A rapidly developing, slightly less transparent, and bluish-white looking emulsion.

Grade C: Fine milky emulsion that forms in under two minutes.

Grade D: A dull, grayish-white emulsion that seems slightly greasy and takes a long time to emulsify (more than two minutes).

Grade E: The formulation shows either little or poor emulsification with large oil globules present on the surface.

When distributed in GIT, Grade A and Grade B formulations will remain as nano-emulsions. While Grade C formulations may be recommended for SEDDS formulation.

1.7.10 Cloud Point determination: Typically, the cloud point is calculated by gradually raising the temperature of the water bath into which the formulation is applied and spectrophotometrically measured. The cloud point, or temperature above which a clear solution becomes hazy, is the point at which the permeability in percent starts to decline. The temperature is 37 °C; in order for formulations to maintain their self-emulsifying capabilities, they must have a cloud point greater than body temperature. Phase separation and poor drug solubilization are frequently seen at temperatures over the cloud point because the surfactant is prone to dehydration. The drug's lipophilicity and other formulation elements have an impact on the cloud point.

1.7.11 Measurements of Viscosity: The diluted SMEDDS formulation, which is a micro-emulsion, is typically assessed for its viscosity using rheometers like the Brookfield rotating spindle viscometer or the Brookfield cone-plate rheometer with conical spindle. The initial increase in viscosity followed by a decrease during the International Journal of Pharmaceutical Sciences and Research 4839 titration, where the increase in water volume is caused by the water percolation threshold, indicates the formation of an O / W micro-emulsion from a W / O micro-emulsion with an intermediate bi-continuous phase. The diagram between shear stress and shear rate can be used to estimate the micro-emulsion's rheology. The behavior suggests that there are tiny, spherical droplets present.

1.7.12 Dilution studies: By dilating the microemulsion pre-concentrate, the impact of dilution on the microemulsion's clarity can be determined. in a variety of diluents, including double distilled water, simulated gastric juice (SGF), and simulated intestinal juice (SIF) 94, in various dilutions that imitate gastrointestinal circumstances. If the clarity remains unchanged while the dilution and type of diluent are increased, medication precipitation has not occurred. SMEDDS can mimic in-vivo conditions when diluted 100 times with all of the diluents indicated above 95. By dilution SMEDDS with various solvents, such as buffer pH 1.2, buffer pH 6.8, etc., along with distilled water, the influence of the dilution medium's pH value may be investigated, and the transparency and effectiveness should be observed.

1.7.13 Percent Transmittance: This test reveals whether the diluted SMEDDS formulation is transparent. It is established water is preserved as a blank value and the formulation is measured spectrophotometrically after being diluted with water. A clear and transparent microemulsion has formed, as shown by the transmission percentage figure that is near to 100%.

1.7.14 Differential Scanning Colorimetry: This technique is mostly used to describe the properties of micro-emulsions made by diluting SMEDDS with peaks that correspond to water. The peaks reveal whether or not the water is in a bound or free state. As a standard, pure water displays a big, abrupt peak at about -17 ° C, signifying the freezing point. The presence of the bound state in micro-emulsions, preferably bound to surfactants, is demonstrated by Podlogar et al.'s DSC experiments on water micro-emulsions, isopropyl myristate system Tween 40 which identified peaks that correspond to water at a lower temperature than pure water (approximately -45'C at 15% W/W). The temperature changes when the water concentration is greater than this. They came to this conclusion from the observations of thermal water behaviors.

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