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# A REVIEW ON SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEM-PROMISING LIPID BASED APPROCH TO ENHANCE SOLUBILITY OF POORLY SOLUBLE DRUG

**PATEL JK[1*], PATEL GK[2], PATEL D[3], PATEL J[4] AND SUTHAR D[5]**

**1:** Department Of Pharmaceutics, Shree S K Patel College of Pharmaceutical Education and Research, Ganpat University, Kherva -384012, Gujarat, India

**2:** Department Of Pharmaceutics, Shree S K Patel College of Pharmaceutical Education and Research, Ganpat University, Kherva -384012, Gujarat, India

**3:** Department Of Pharmacognosy, Sharda School of Pharmacy, Pethapur, Gandhinagar-382610 Gujarat, India

**4:** Department Of Pharmaceutical Analysis, Sharda School Of Pharmacy ,Pethapur, Gandhinagar- 382610 Gujarat, India

**5:** Department Of Pharmaceutics, Sharda School of Pharmacy, Pethapur, Gandhinagar- 382610 Gujarat, India

***Corresponding Author: Ms. Jaini K. Patel: E Mail: pateljainipharma22@gmail.com**

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## ABSTRACT

Self micro-emulsifying drug delivery systems (SMEDDS) are a proven method for poorly soluble substances works by increasing the solubility and bioavailability. SMEDDS and isotropic mixtures, are composed of oils, surfactants, and occasionally cosolvents. The ability of these formulations and methods to produce microemulsions or fine oil-in-water (o/w) emulsions after moderate stirring and dilution by water phase along the GI tract might be a promising technique for lipophilic agents with dissolution rate-limited absorption**.** By integrating suitable polymer into the formulation, SMEDDS maybe studied for the creation of a formulation with sustained drug release. This technology's improvement might lead to a new

application in the field of medicine delivery. SMEDDS has beendemonstrated to be quite efficient in increasing oral bioavailability of lipophilic products**.** SMEDDS is one of the promising methods for controlling the characteristics of medications that are not great choices for oral delivery **.** It is also worth mentioning that SMEDDS may be made invariety of solid dosage forms that are acceptable for both oral and parenteral administration. Oral delivery of many proteins and medical peptides is limited. Due to the GI tract's enzymatic and absorption membrane limitation, technologies have been investigated to solve these obstacles. SMEDDS from the last few years have acquired much interest as prospective carriers for oral peptide and protein administration **.** This review provides an outline of SMEDDS's numerous advances and biopharmaceutical elements, types, manufacturing, characterization, limitations, and future prospects. The evaluation of SMEDDS and its applicationsare also discussed, focusing on the advances of SMEDDS's solid self micro-emulsifying delivery mechanism and dosage form.

**Keywords: SMEDDS, Solubility enhancement, L-SMEDDS, S-SMEDDS, lipid based Oral delivery**

## INTRODUCTION

Emulsions serve as drug carriers in pharmaceutical preparations even though they can likely improve the medicine's oral bioavailability by having poor absorption profiles **[1]**. The prominent strategies for enhancing the stability of orally administered APIs are to use delivery systems of drugs that are based on lipids **[12]**. According to the literature, the terminology for lipid-based techniques is highly debated. The initial droplet size is not the primary factor determining micro and nano emulsions (SMEDDS and SNEDDS) **[10]**. If the droplet size of emulsion is in the nanoscale range, the SNEDDS term should be used. SEDDS are oil and surfactant-based preparations with the help of slow agitation that can be emulsified rapidly in water. The chemical structure and physical properties of SMEDDS physical qualities were essential determinants of application and tolerance. As a result, these variables must be established at the stage of Preformulation **[11-13]**.

## MECHANISM OF SMEDDS:

In emulsification process the free energy (ΔG) associated is given by the equation: [17] $\Delta G = \sum N i \pi r i$, In which N‘ is Number of droplets with radius r‘ and σ‘ is interfacial energy. It is apparent from equation that the spontaneous formation of the interface between the oil and water phases is energetically not favored **[13]**. The system commonly classified as SEDDS have not yet been shown to emulsify spontaneously in the thermodynamic sense. The process of self-emulsification was observed using light microscopy. Pouton has argued that the emulsification properties of the surfactant

may be related to phase inversion behavior of the system. For example, on increase the temperature of oil in water system stabilized using nonionic surfactant; the cloud point of the surfactant will be reached followed by phase inversion. The surfactant is highly mobile at the phase inversion temperature; hence the o/w interfacial energy is minimized leading to a reduction in energy required to cause emulsification **[11]**. The specificity of surfactant combination required to allow spontaneous emulsification may be associated with a minimization of the phase inversion temperature, thereby increasing the ease of emulsion **[14]**. Phase studies are also necessary for liquid crystal formation in self-emulsification. In the phase diagram of the system (30 % w/w tween and 85/70 % w/w MCT oil) for dilution in water over a range of temperature shows that the phase inversion region is at approximately 40° C and the system works well at ambient temperature up to 60°C above which water in oil emulsion tend to form **[18]**. The emulsification process may be associated with the ease with which water penetrates the oil-water interface with the formation of liquid crystalline phases resulting in swelling at the interface thereby resulting in greater ease of emulsification **[9]**. However, for system containing co- surfactant, significant partitioning of components between the oil and aqueous phases may take place leading to a mechanism described as ―diffusion and stranding, where by the oil is solubilized, leading to migration in to the aqueous phase **[18]**.

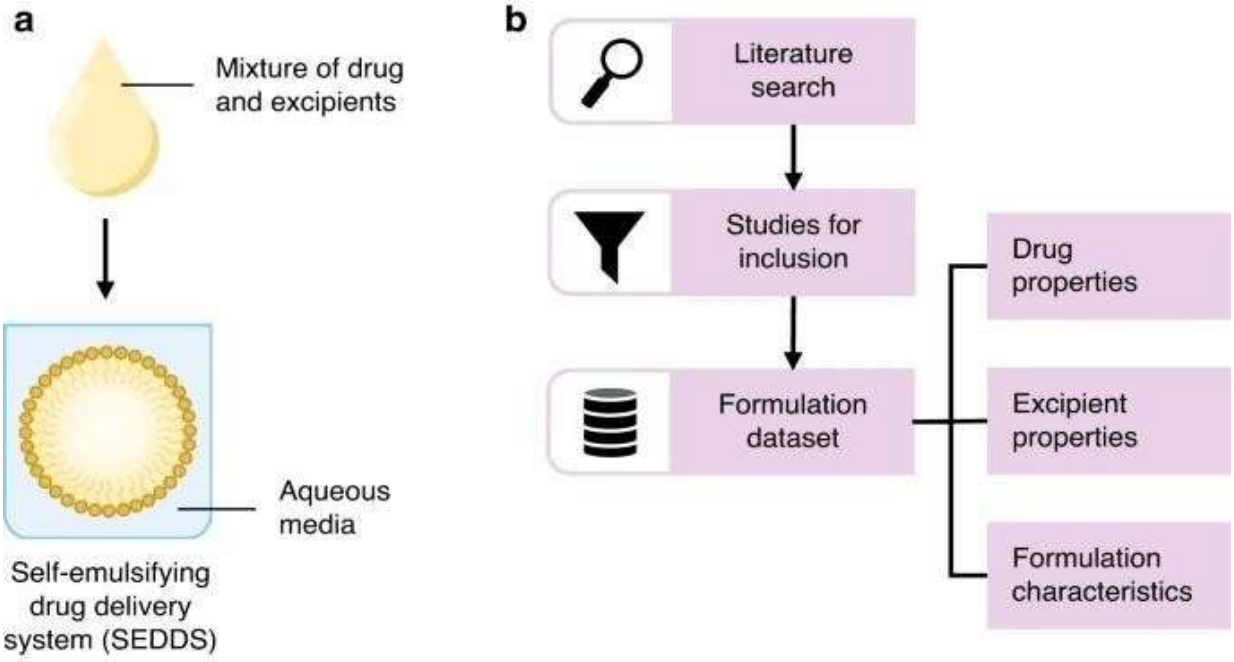


**Figure 1: Basic of SMEDDS**

**Figure 1** shows information obtained for an individual sample in the dataset included theidentity and relative proportion of the drug, as well as each individual excipient (i.e., oils, surfactants, cosolvents, and other ingredients). Other additives or ingredients were grouped by function (e.g., absorption enhancer, precipitation inhibitor, etc.), as opposed to the individual identity, to facilitate downstream analysis **[6]**. The proportions of each component for a given formulation were standardized as compositional data, such that they totaled to 100% in units by weight. Additional descriptors included the average particle size (i.e., droplet diameter of SMEDDS upon dispersion) and average droplet polydisperse index, whereapplicable. A manually defined descriptor denoting whether a given formulation was found to be promising in the context of its source article was also included. A formulation was considered to be promising if it wasselected for further development and/or exhibited the most favorable properties (i.e., dependent on the original study) from a panel of screened formulations **[2-4]**.

Due to the various possible limitations with the GI system, hydrophilic macromolecular medicines, proteins primarily polysaccharides, therapeutic peptides, and DNA-based therapies, have low oral bioavailability. A range of tactics has been used to address this issue, including structural drug changes, addition of auxiliary agents, and the production of SMEDDS Nano carriers, which are used in various studies as a prominent term for both self-nano- and self-micro emulsifying drug delivery systems (SNEDDS/SMEDDS) and emerge to be a successful method for oral medicines **[12]**. The preparation of SEDDS on an industrial level is economical and simpler than other Nano carriers, including liposomes, micelles, polymer- based nanoparticles, carbon nanotubes, or noisome, because it is almost like the solution preparation **[8]**.

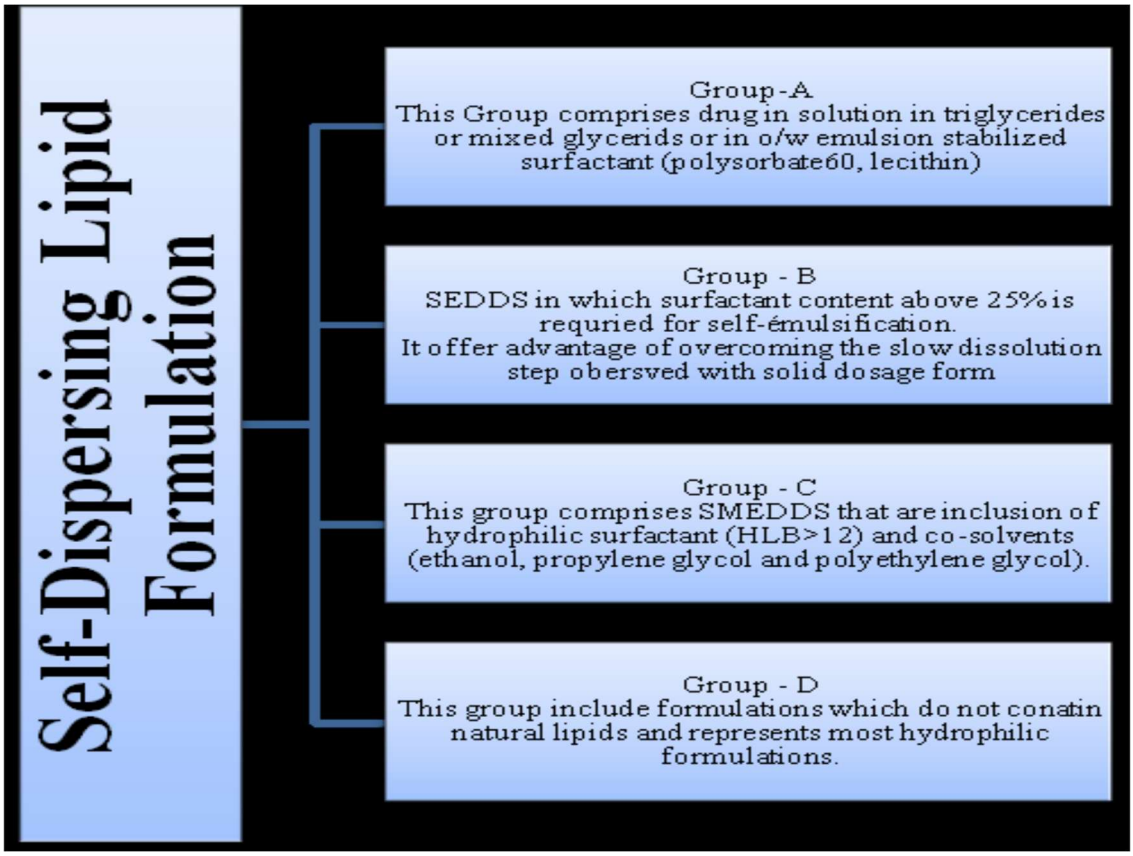


**Figure 2: Flow chart for Self-Dispersing lipids Formulation**

Self-emulsification is influenced by the quality and nature of the concentration of surfactants, pair of oil/surfactant, and oil/surfactant ratio, and the physiological parameters in which it happens, including pH, and temperature **[3]**. SMEDDSs vary from conventional oral drug delivery systems in that digestion of enzymes significantly changes the excipients in the formulation. Gastric and pancreatic lipases hydrolyze the lipids in the oil phase of SMEDDSsin the GIT, releasing additional amphiphilic lipid digestion products. The solubilization of biliary lipids secreted in the bile is quick and these released digested lipids **[4]**. Different parameters are linked with the gastrointestinal lipolysis process during lipid digestion. These parameters include pancreatic and gastric lipase secretions, the difference in the small intestine's pH in and the stomach, pH of the lipase action, and secretions of the bile that allow solubilization of micelle by lipolysis products.

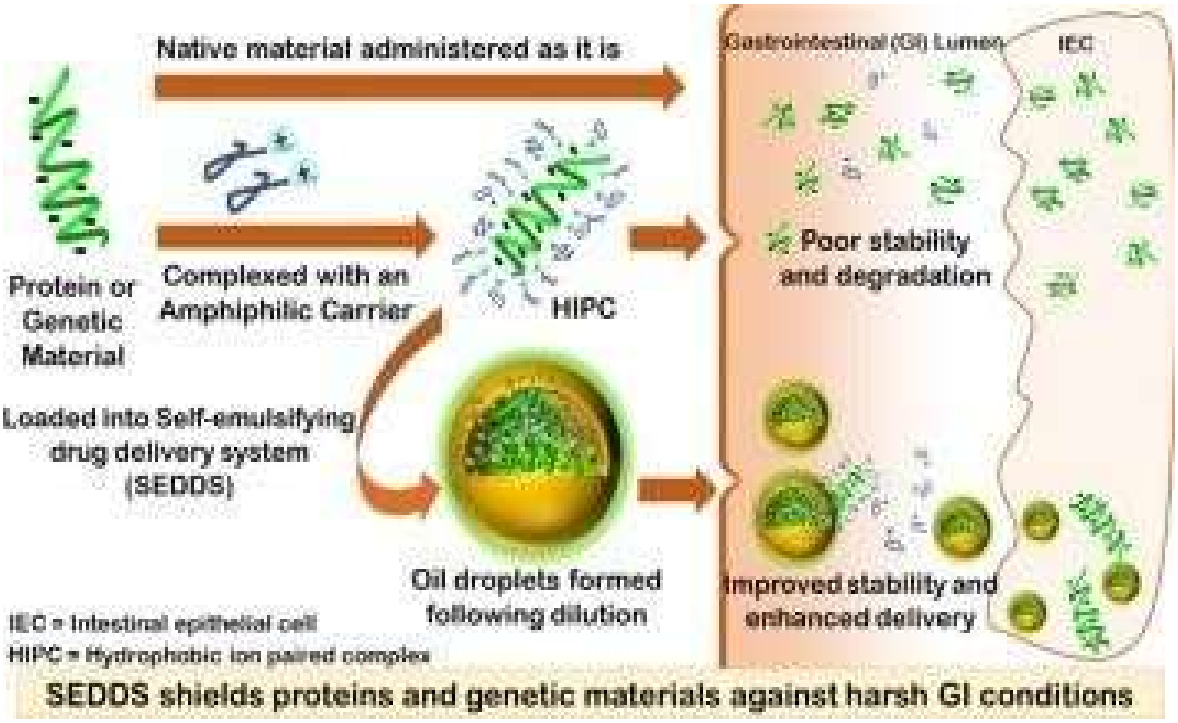


**Figure 3: Mechanism of SMEDDS IN GIT**

**Figure 3** indicate SMEDDS have also been established to administer hydrophilic macromolecular medications orally like pDHA, peptides, proteins, and polysaccharides throughout the years. The resultant combinations can be integrated into the lipophilic phase of SMEDDS because of hydrophobic ion pairing (HIP) with charged auxiliary agents that is lipophilic in nature. By utilizing auxiliary agents in suitable proportions for the HIP, drug release was deliberately modified according to the solubility of the compound in the SMEDDS pre-concentrate and the release matrix Based on the target region, the oily droplets might be either mucoadhesive or very mucus permeable. Additionally, coating them with peptides that are cell penetrating, by altering their zeta potential, and their cellular absorption capabilities may be fine-tuned. Meanwhile, several *in vivo* experiments exhibiting bioavailability in the percentage range of single digit have demonstrated SMEDDS' potential for oral administration of hydrophilic macromolecular medications. Due to these characteristics, modified SMEDDS has shown to be a recent approach of assessment for the administration of hydrophilic macromolecular medications orally.

Phosphate groups from the surface of SMEDDS and altering zeta potential from negative to positive, the shift was rather slight, ranging from −1 to +1 mV in the best scenario.

Moreover, excipients like octylamine, cetylpyridinium, or cetrimonium, can be included from a safety standpoint to have positive charges on SMEDDs surface that was accessible after the cleavage of phosphate group. Furthermore, because both surfactants (cationic or anionic) were to be included in the same formulation, unwanted ionic interactions, including ion pairing, could not be ruled out.

Apart from common methods like dispersibility tests, turbidimetric evaluation, and viscosity tests, complex instrumental requirements like photon correlation spectroscopy (PCS) or dynamic light scattering (DLS), electro kinetic potential measurement, nondestructive spectroscopic techniques (LFDS, FTIR, RS), and numerous microscopic methods (SEM, PLM,EDS) have been defined. To achieve the greatest value, outstanding bioavailability, and tolerance of the dosage forms for human administration, all significant aspects must be identified during the preformulation stage of self-emulsifying drug delivery systems (SMEDDS) **[9]**.

**Benefits of SMEDDS as compared to conventional emulsio**

Benefits of SMEDDS include its easy manufacturing by the basic instrument rather than high cost and specialized equipment required by the suspension and emulsion for the monitoring of analytical procedures including rate, intensity, and mixing duration Transforming liquid **[6]**.

SMEDDS into solid dosage forms, which impart physicochemical stability and lower manufacturing expenses while keeping the pharmacokinetic advantages associated with lipids, is a typical strategy used to address these basic short comings **[8]**. For solid-SMEDDS development, various approaches of solidification can be used including; *in vivo* emulsification, pre-emulsification, and then *in vitro* stabilization which allows GI tract redispersion of emulsion. Solid-SMEDDS may be developed using a variety of solidification techniques, that can be divided into those that (i) emulsify *in vivo* and (ii) are pre-emulsified and stabilized *in vitro*, enabling for emulsion redispersion throughout the GI tract. Solidification may provide a variety of biological benefits to the SMEDDS formulation in this way. Solidification can provide a variety of biologicalbenefits to the SMEDDS formulation including:

**Prolonged gastric residence**

Polymers like HPMS and microcrystalline cellulose are responsible for the extension of overall transit and gastric emptying time. It causes helpful interactions with epithelial cells

of stomach by incorporation of floating excipients which leads to enabling of formulations to be buoyant with the gastric media **[5]**. This prolongs the total disintegration period as well as the time available for absorption.

**Improved intestinal solubility**

There are varieties of methods, such as stabilizing supersaturated drug states and regulating digestible lipids' lipolysis, solidification of SMEDDS can increase intestine solubility. Polymeric nanoparticles can be utilized as polymeric precipitator inhibitors (PPIs) for retaining the supersaturated state of solubilized molecules of drug. It also alters the functioning of digestive enzymes by altering in the chemistry and nanostructure of surface of the carrier material. As a result, the precipitation inhibitory action and solubilizing mechanism of lipolysis products increase encapsulated medicinal molecules' intestinal solubility **[1]**.

**Improved drug permeability**

Mucoadhesive polymers and chitosan, well-known solid-state intestinal permeation boosters are used to manufacture SMEDDS to improve medication permeability through the intestinal epithelium. For improvement of permeability, there has been little research on solid-SMEDDS. Studies have shown that attachment of silicates with liquid-SMEDDS improves intestinal drug permeation, indicating the ability for solid-SMEDDS to have potential to deliver class IV drug compounds **[4]**.

**Lipid-based oral delivery**

According to current parameters, the therapeutic effectiveness of an oral route of administration is increasing. Aqueous solubility, dissolution, and permeability are some of these parameters. As per Biopharmaceutical Classification System (BCS), drugs are identified as class II (low solubility,high permeability) or class IV (low solubility, poor permeability **[2]**. To address all of thesechallenges, new technologies in the form of innovative dosage forms have been created. It is largely directed at pathogens or diseased cells. Lipid-based formulations increase medication solubilization during GI transit and provide a lipophilic microenvironment to facilitate drug delivery to intestinal absorptive regions. The self-convening ability of lipid has been used to explain several colloidal drug carriers with various structures, including emulsions, micelles, microemulsions, liquid crystalline nanoparticles, vesicular carriers such as solid lipid nanoparticles, liposomes, noisome, polymer–lipid hybrid nanoparticles, and SMEDDS **[3]**.

Table 1: Typical properties of Type I, II, III and IV lipid formulations

| Formulation Type | Materials | Characteristics | Advantages | Disadvantages |
|---|---|---|---|---|
| Type I | Oils without surfactants (e.g: tri-, di- and monoglycerides) | Non-dispersing, requiresdigestion | Generally recognized as safe(GRAS) status; simple; excellent capsule Compatibility | Formulation has poor solvent capacity unless drugis highly lipophilic |
| Type II | Oils and water-insoluble surfactants | SEDDS formed without water-solubleComponents | Unlikely to lose solventcapacity on dispersion | Turbid o/w dispersion(particle size 0.25–2 μm) |
| Type III | Oils, surfactants, cosolvents (both water-insoluble andwater-soluble excipients) | SEDDS/SMEDDS formedwith water-soluble components | Clear or almost clear dispersion; drug Absorptionwithout digestion | Possible loss of solvent capacity on dispersion. less easily digested |
| Type IV | Water-soluble surfactants and cosolvents (no oils) | Formulation dispersestypically to form a micellar solution | Formulation has good solvent capacity for manydrugs | Likely loss of solvent capacity on dispersion; maynot be digestible |

## Biopharmaceutical issues

It is worth noting that lipids such as triglycerides can influence the oral bioavailability of drug by changing biopharmaceutical features such as improving dissolution rate and enhancing solubilityin the intestinal fluid, chemical protection of the drug and enzymatic deterioration in oil droplets,and promoting lymphatic transport of highly lipophilic drugs by forming lipoproteins. The pattern of drug absorption and blood/lymph circulation are influenced by degree of saturation, chain length of, and volume of the lipid.

## Specificity

Self-emulsification depends on the ratio of oil/surfactants, its nature of pair, concentration of surfactants, and self-emulsification temperature. Self-emulsifying system (SES), is usually fulfilled through limited and specific combinations of pharmaceutical excipients. The specific physicochemical compatibility of the drug determines the success of the incorporation of the druginto a SMEDDS. That is why study of phase diagram and preformulation solubility is needed to prepare suitable formulation design

## Excipient selection

Self-emulsification is very definite to the nature of the combination of surfactant and oil, the concentration of surfactant and ratio of oil and surfactant as well as the temperature of the occurrence of self-emulsification.

Following the identification of a list of possible excipients, a binary drug–excipient screening for stability, compatibility, and solubility, should be performed to determine the most suited lipid system for the drug in

issue. When designing SEDDS/SMEDDS that utilize various excipients, overall solubilizing power of the system should be focused rather than the solubility of the drug inthe individual components, even though assessment of affinity and solubility of the drug for each component is essential. Surfactant, co-surfactant, and oil phase components might be synthetic, semi-synthetic, or natural but components are chosen because of

(1) attaining maximum loading of drug,

(2) to ensure maximum absorption, duration of self-emulsification and droplet size must be kept to a minimum in the gastric environment,

(3) to decrease droplet size of emulsion, fluctuation as a function of aqueous medium pH and electrolyte concentration, and

(4) to avoid/reduce medication degradation/metabolism in the physiological environment.

## MATERIAL OR COMPONENTS OF SMEDDS

**Drug:** To expand the bioavailability of the medication and to diminish molecule size, the portion ought to be low mainly<40mg. The drug is formulated at a modest dose and should not be subjected to substantial first-pass metabolism. The medication ought to be insoluble in water. The log P ought to be more noteworthy than 4 (lipophilic), high dissolvability in LCT for lymphatic assimilation (>50mg/ml). BCS class II and IV

**Oil**: Oil is necessary for the lipophilic drugs solubilization. It improves the drug's availability for quick absorption in the GI tract via the intestinal lymphatic system. The degree of esterification and kind of fatty acids and with regard to glycerol to create mono or diglycerides determine the physical, melting, and hydrophilic–lipophilic balance (HLB) features of glycerides.

**Surfactant and co-surfactant**

Surfactants lower the interfacial tension by forming an interfacial film, allowing for dispersion. During SMEDDS formulation, the HLB value must be kept in mind. A surfactant with an HLB value greater than 12 is chosen to achieve better emulsification. It helps to disseminate the intended formulation quickly by forming small oil-in-water (o/w) droplets. Nonionic surfactants are commonly used in the formulation of SMEDDS due to their nontoxic nature, despite the fact thatthey may produce a modest irreversible change in the permeability of the GIT wall. In GIT, a formulation of surface-active compounds that is 30–60% w/w results in improved self-emulsification. Surfactants in high amounts might irritate the wall of the GI tract.

Co-surfactant lowers the transitory negative value of interfacial tension even further. It gives the interfacial film flexibility so that varied curvatures can be achieved for the creation of different microemulsions concentrations. By adding co-surfactant, the higher amounts of surfactant (approximately 30%) can be simulated.

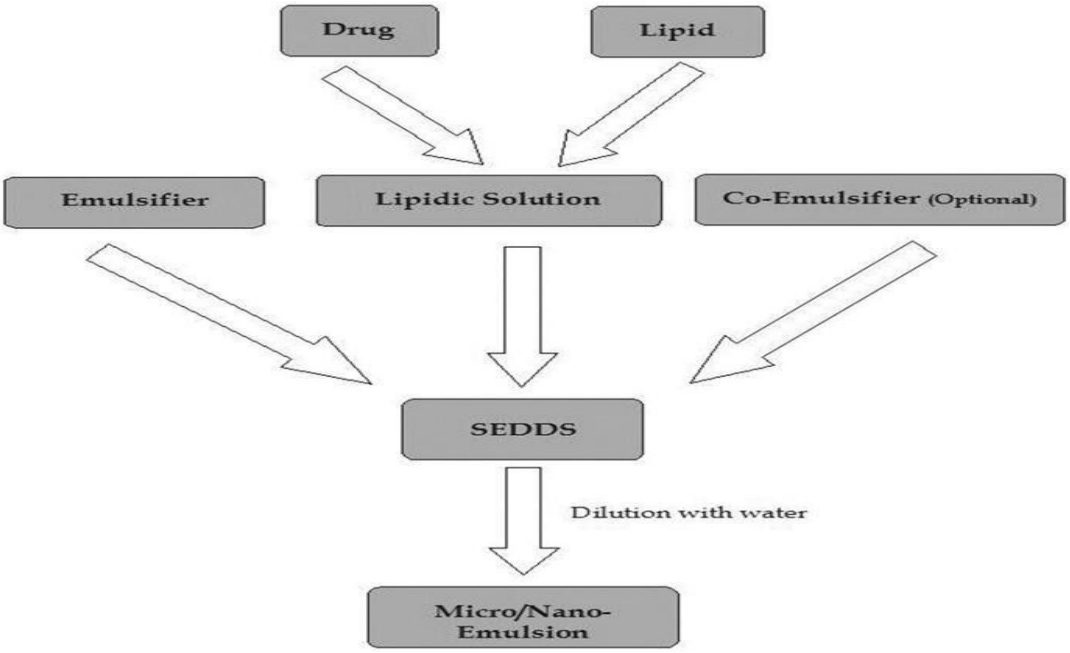


**Figure 4: Micro emulsion preparation**

**METHOD OF PREPARATION OF LIQUID SMEDDS:**

- High pressure homogenizer
- High energy approach
- Micro-fluidization
- Sonication method

**Conversion of liquid SMEDDS to Solid SMEDDS:**

A very well-designed system is required for the stabilization of administration of macromolecules through oral route as it is difficult to deliver macromolecules like peptides and proteins. As hydrophilic peptides and proteins tend to precipitate and display structural changes in liquid SMEDDS formulations, S-SMEDDS has the ability to stabilize them. S- SMEDDSs in suppressing first-pass metabolism and P-gp efflux, lymph targeting, and regulated release are all discussed in detail.

**Encapsulation of liquid and semi-solid self-emulsified formulation:**

This is a simple, common approach for loading low doses of highly potentdrugs. The micro spraying and banding procedure are used to fill capsuleswith liquid self-emulsified

solutions. Excipients are heated to 20 °C or above their melting point for encapsulation of semi-solid self-emulsified preparations. Molten mixture is added to load the therapeutic agent. Then,a capsule shell is taken to be filled with drug molten mixture and allowedto cool at room temperature. Banding or micro spray process is used to seal the filled capsule.

**CHARACTERIZATION OF SMEDDS:**

**Visual evaluation**

Visual observation helps in the assessment of self-emulsification. The existence of a clear, isotropic, transparent solution after water dilution of SMEDDS suggests microemulsions production, whereas an opaque, milky white appearance indicates macro emulsion evolution. A lack of precipitation and/or phase separation suggests that the formulation is stable.

**Analysis of droplet size**

The size of the droplet is determined by the surfactant's type and concentration. The microemulsions generated during dilution of SMEDDS with water has a very narrow droplet sizedistribution, which is critical for optimal drug release, *in vivo* absorption, and stability. Droplet size analysis is done using DLS methods.

**Zeta potential measurement**

The zeta potential reflects the emulsion's stability following dilution. If the zeta potential is larger, the formulation remains stable. When compared to particles with either surface charge, particles with a zwitterion charge exhibit greater biocompatibility and a longer blood residence period.

**Emulsification time**

The amount of time it takes to emulsify a formulation is determined by the oil/surfactant and oil phase ratio. This is determined using a basket dissolution equipment, which observes the development of a clear solution under agitation following drop wise formulation addition to a water-filled basket.

**Cloud point determination**

The cloud point of a homogeneous solution is the temperature at which it drops its transparency. Above the cloud point, the surfactant normally loses its ability to form micelles. It is determined by progressively raising the temperature of the formulation and spectrophotometrically detecting the turbidity. The cloud point of the surfactant is the temperature at which the percentage transmittance decreases. To maintain self-emulsification, formulations should have a cloud point higher than 37.5 °C.

**Viscosity measurements**

A rheometer, Brookfield viscometer having a cone and plate with rotating spindle is used to assessthe viscosity of diluted SMEDDS

formulations that are microemulsions.

**Liquefaction time**

This analysis is performed to determine how long it takes for S-SMEDDS to melt in a simulated GI environment without moving. The dosage form, which is threaded to the bulb of a thermometer,is covered in a transparent polyethylene film. The thermometer should then be placed in a round bottom flask with 250 mL of simulated stomach juice without pepsin and held at 37 °C. After that,the time it takes for the liquefaction to happen is noted.

**Applications of SMEDDS:**

Lipids, surfactants, and cosolvents make up the SMEDDS formulation. The system may form an o/w emulsion when separated by a water phase with modest stirring. SMEDDSs deliver medications in small droplets with a balanced distribution, resulting in improved dissolution and permeability. As medicines can be loaded in the inner phase and supplied via lymphatic bypass sharing, SMEDDSs protect drugs from enzymatic hydrolysis by in the GI tract and decrease presystolic clearance in the GI mucosa and hepatic first pass metabolism **[14]**.

**CONCLUSION**

SMEDDS is an incredible and valuable methodology for the preparation of drug compound with poor solubility, pre-systemic first-pass impact, high atomic weight, gastric irritation, enzymatic degradation, low rate of dissolution, and low bioavailability. This methodology is appropriate for all medications of BCS since arranged emulsion gives quicker absorption, faster dissolution rates, and high bioavailability because of solubilization of medication in lipidic excipients which dodges the dissolution step. This methodology needs more misuse in field of SEOPT plans and other dosage form. They need IVIVC which should be broad and constant correlation these investigations in not so distant utilizing bio relevant media.

**Table 2: Examples of Marketed SEDDS Formulations**

| Drug Name | Compound | Dosage form | Company | Indication |
|---|---|---|---|---|
| Neoral | Cyclosporine | Soft gelatin capsule | Novartis | Immune suppressant |
| Norvir | Ritonavir | Soft gelatin capsule | Abbott Lab | HIV antiviral |
| Convulex | Valproic acid | Soft gelatin capsule | Pharmacia | Antiepileptic |
| Lipirex | Fenofibrate | Hard gelatin Capsule | Genus | Antihypertensive |

**Table 3: Examples of SEDDS for Oral Delivery of Lipophilic drug**

| Type of delivery system | Oil | Surfactant | %w/w | Solvent(s) | Drug | Drug content |
|---|---|---|---|---|---|---|
| SEDDS | A mixture of mono- and di-glycerides ofoleic acid | Solid, polyglycolyzed mono-diand triglycerides, Tween 80 | 80 or 20 | - | Ontazolast | 7.5 |
| SEDDS | Olive oil | Polyglycolyzed glycerides | 30 | Ethanol | CsA | 10 |
| SEDDS (positively charged) | Ethyl oleate | Tween 80 | 25 | Ethanol | CsA | 10 |
| SEDDS (positively charged) | Ethyl oleate | Tween 80 | 25 | Ethanol | Progesterone | 2.5 |
| SEDDS | Myvacet 9- 45 or captex 200 | Labrasol or Labrafac CM10 | 5-30 0-25 | - | CoQ10 | 5.66 |
| SEDDS(Norvir) | Oleic acid | Polyoxyl 35, castor oil | NA | Ethanol | Ritonavir | 8 |
| SEDDS (Fortovase) | dl-alpha tocopherol | Medium chainmono-and diglycerides | NA | - | Saquinqvir | 16 |

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