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REVIEW ARTICLE

Self-Micro Emulsifying Drug Delivery System (SMEDDS): A Review on Biopharmaceutical Aspects and Physico-Chemical Aspects

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ABSTRACT
Self-micro emulsifying drug delivery system (SMEDDS) is distinctive system in development for high and intra-head variability, low bioavailability and the absence of dose weight associated with hydrophobic drugs because of their immense capability in BCS II and IV class drugs to improve their low aqueous solubility. Different characterization parameters distinguish such as visual assessment, polarity of droplets & emulsion drop size, dissolution test, charge on lipid drops, consistent findings and in vitro diffusion analysis. This review also describes the SMEDDS preparation and discusses the construction of the SMEDDS pvT diagram, explaining the process include in self-emulsification and biopharmaceutical and physicochemical aspects. SMEDDS has to empower new uses in delivery of drugs.
Keywords*: Ternary phase diagram, biopharmaceuticals, physicochemical, bioavailability.*

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INTRODUCTION

In the past few years, the focus is on oral dosage form by the SMEEDS for enhancing the solubility and absorption of poorly water soluble drugs [1]. The different techniques improve the oral bioavailability of poorly water soluble drug [2]. Oral administration of 50% of drug combination is prevented due to high lipophilicity of drug [3]. About forty percent novel drugs show poor aqueous solubility, leading to absence of dose determination, high inter intra subject variance & poor oral bioavailability [4]. SMEEDS is an isotropic compound of natural or synthetic oils which have the capacity to get pure oil in water (o/w) on slow stirring [5]. Most of BCS class II have poor aqueous solubility & high permeability leading to low oral bioavailability, high intra inter subject variation, absence of hydrophobic drug dosage proportionality [6]. Today a technical figure is present to assign drugs with poor solubility, dissolution rate and bioavailability of insoluble drugs [7].

The self-micro emulsifying drug delivery system (SMEDDS) or self- emulsifying drug delivery system (SEEDS), which enhances entrance and availability of hydrophobic drugs by preventing them from entering first pass metabolism, are two techniques to improve hydrophobic drug dissolution [8]. Hydrophobic drug disperse in oil is prepared in this way. The SEEDS contains oil that must be less than 100nm size droplets [9]. SMEDDS interacts with GI lumen and forms w/o micro emulsion with GI fluid. It is best for weakly water-soluble drugs with lipid as carriers & surface active agents that form w/o micro emulsion within GIT lumen [10]. [Fig: 1].

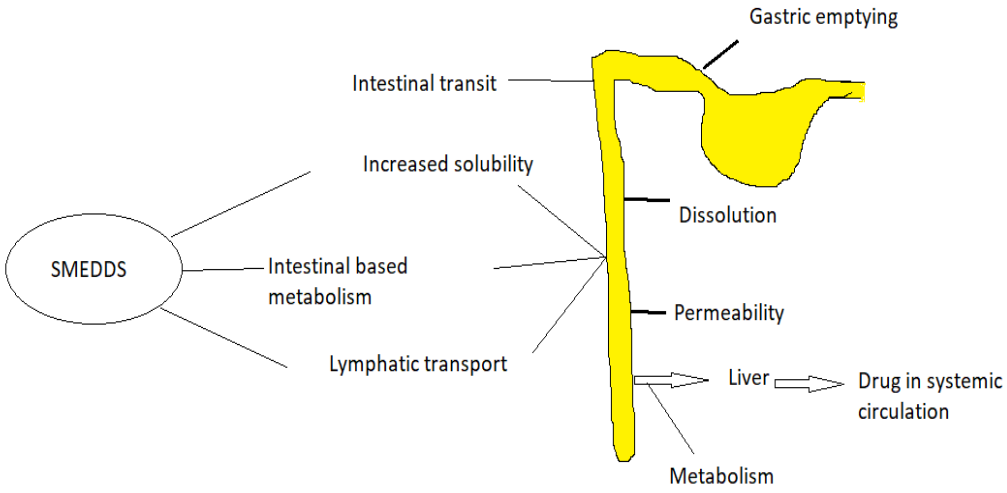

Fig: 1 SMEDDS improving bioavailability of drugs through oral absorption

Micro-emulsion History:

Hoar TP first coined the term "micro emulsion" and Shulman JH., Professor of Chemical Engineering at the University of Cambridge, 1943. Other topic used local unit for those systems, such as dilate micelle and solubilized oil.[11]

This space unit is usually met with selection of components, limited dimensions and "co-surfactant" that provides the flexibility to o/w interface.

This condition exhibits a thermodynamically improved configuration, which is stable against conventional emulsions and is not essential for high-energy input (i.e. by stirring) to form.[4]

In comparison with the emulsions, which are a unit of space for sensitive and stable reaction forms, the local unit of SMEDDS is a stable physical structure that is easy to prepare [Fig : 2].

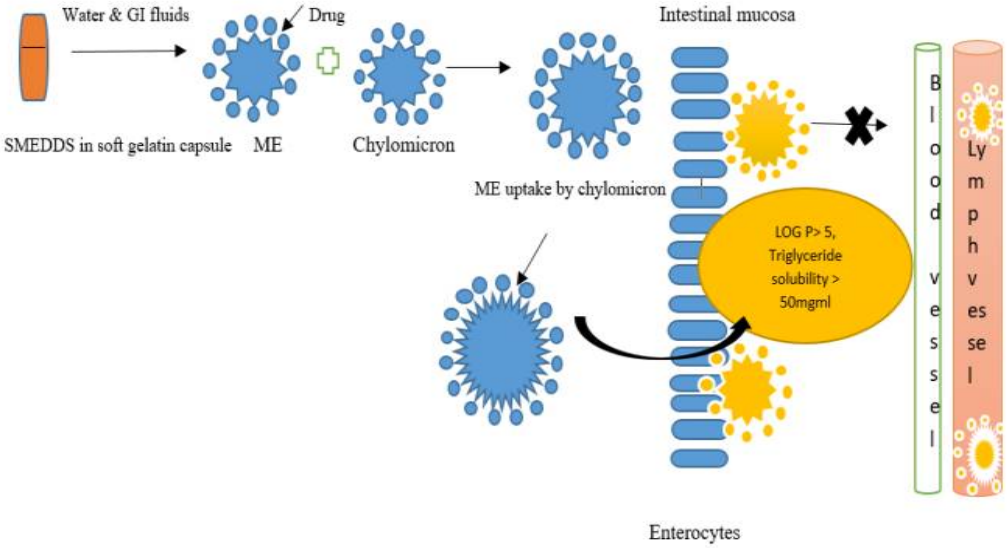

Fig : 2 Lymphatic uptake of SMEDDS

ADVANTAGES OF SMEDDS

- Improved oral bioavailability [3].
- Peptide release capabilities tend to enter enzymatic hydrolysis into GIT.
- Prolongs drug release.
- Effective for both liquid and solid dosage forms.
- Increased drug loading capacity.

DISADVANTAGES OF SMEDDS

- Other mutations will be established in vivo-in vitro relationships so many lipid-based lipid formations should be made with help of suitable animal model in vivo test were performed.

- Process involves a variety of chemical reactions and high levels of surfactants in the formulation [12].
- The desire for the drug to be absorbed after dilution can be greater because of effect of the dilution of hydrophilic solvent.
- Formulations of few parts are very difficult to validate.[1]

FACTORS INFLUENCING SMEDDS FORMULATION

The various elements that affect the structure of SMEDDS are listed below:

1. The lipophilic phase polarity

It controls release of drug from emulsions. HLB value determines the globule polarity [14].

2. Drug's Dose and Nature

Higher dosage formulationis not acceptable in SMEDDS unless it is easily soluble in atleastone component of formulation. Drugs within limited lipid solubility are difficult to deliver via SMEDDS.

3. Charge on globule of emulsion

Most of the time, negative charging occurs in the formulation that results in electrostatic repulsive force. Positive can be obtained in few formulations [15].

4. Equilibrium solubility measurement

This was completed in anticipation of possible case of precipitation in the GI study Pouton's found that the preparation in which crystallization forms could take 4-5 days to obtain a equilibrium and drug could be left over 24 hours in supersaturated state after initial emulsification process [16].

SMEDDS APPLICATION:

- **Solubilization in SMEDDS**

Because of its high oil content in general, in addition to being a surfactant, SMEDDS tends to combine solvents with a spectrum of lipophilicity. Therefore, solubilisation volume of w/o microemulsion of soluble drugs is commonly greater than that of o/w micro emulsion, but inverse is correct for oil soluble drugs. In addition, solubilization activates SMEDDS formation [17].

- **Defence against biodegradation**

Several drugs are impaired in physiological process due to acidic pH of GIT etc. Drugs like that, if made into SMDDS varieties, may be shielded from degradation processes as liquid crystalline innovate SMEDDS can be associated with quality, acting as obstacle between the degrading nature and the drug [18].

- **Drug Release Control**

Making and stabilization of nanocrystalline form of a drug may cause economic and process problems. That information improves bioavailability due to improved drug solubility and reduced intestinal irritation [19].

- **Improving the bioavailability of drug**

Most drugs are naturally lipophilic so, they should not be soluble in water. The lipophilic drug should have low bioavailability. In SMEDDS, drugs should be mixed with oil and complex so that the oil can be easily absorbed by the intestines and increase the drug solubility. Therefore increase the bioavailability of the drug [20].

SMEDDS FORMULATION

The formulation process of SMEDDS is represented in flow chart.

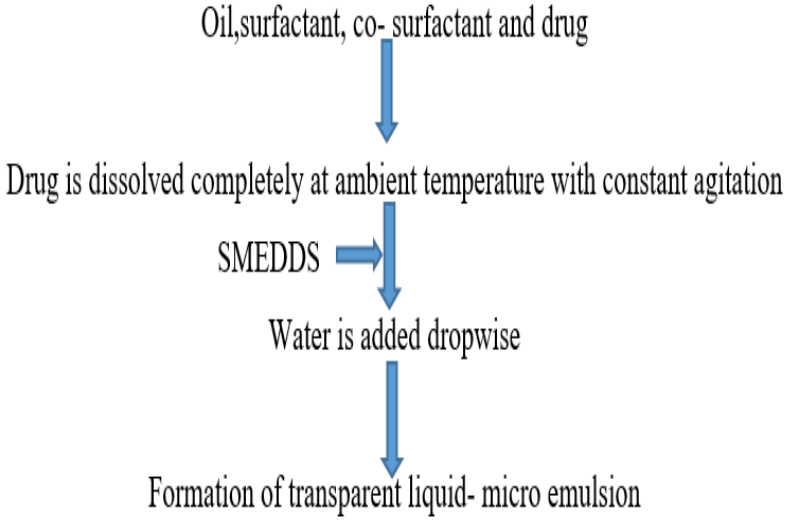

Fig: 3 SMEDDS formulation process

1. Lipid (Fat)

Lipids are responsible for solubility of hydrophobic drug, cell membrane flow, to improve the speed of dissolution and solubility of the intestinal fluid (GI), and to prevent drug from chemical & enzymatic damage by alteration in drug possession.[3]

2. Surfactant

They play a major role promoting hydrophobic drug solubility in oil, liquid carriers dispersion on dilution in GIT liquids, improving bioavailability by levelling uppermeability, preventing precipitate formation inside GI lumen & increasing substance presence in a soluble form, resulting significant absorption & 30 to 60% concentration is used.[4] They merge on the oil-water interface & settled on the inner stage in the emulsion and form a most stable micro emulsion. Separated surfactant molecules are likely to occur in the hydrophobic group environment within a molecule. Main 4 groups are described below:[3]

i. Anionic surfactants: when they have a negative charge in the hydrophilic phase, such as sulfonate (RSO3-) or sulphate (ROSO3). Sodium laurate sulphate, potassium laurate, etc.

ii. Cationic surfactants: when hydrophilic group is positive. Eg. Quaternary ammonium halide

iii. Ampholytic surfactants: (zwitterionic surfactant) has both charges. Eg. Sulfobetains

iv. Non-ionic surfactants: in this hydrophilic group does not carry a charge but finds its solubility in water from a highly polar group such as hydroxyl or polyoxyethylene. Eg. Span, Tweens.

3. Co-surfactant

In SMEDDS, higher concentration of surfactants is essential to decrease of the interfacial tension, which can result in stomach upset which can lead to stomach irritation. That's why, co-surfactant can be used for minimizing the surfactant concentration, remove huge quantity of lipophilic or hydrophilic surfactant in lipid base and reduce oil / water interactions leading to rapid formation of a microemulsion. Co-surfactants with Hydrophile-Lipophile (HLB) values between 10 - 14 are frequently used in combination with surface active agent to reduce interfacial tension to a large area in order to obtain transient negative value & to provide flexibility to the interfacial film. SMEDDS Co-surfactants are listed in below.[23]

SELF-EMULSIFICATION MECHANISM

Self-emulsification happens entropy changes that the dispersion selection is higher than entropy wanted to extend dispersion period so free entropy (ΔG) is negative [24]. Free entropy of micro emulsion formulation, combined with the entropy required to form new surface between two desired phases & expressed in equation (1).

$\Delta G = \Sigma N \pi r^2 \sigma$ ……. (1)

There, ΔG is a free energy related path

N number of globules of radius r once

Σ is the interfacial energy.

Later period of time, two phases of emulsion likely to separate to minimize bonded area and free entropy is reduced.[25] An emulsifying agent is added to stabilize the emulsion which reduces the bonding strength, in addition to giving obstacle to avoid mixing. In SMEDDS, automatic emulsification occurs due to lowest free, positive or negative entropy [26]. Above a certain level of water infiltration, boundary disturbances occur, leading to the formation of droplets [27].

TERNARY PHASE DIAGRAM

Phase diagram is used to ensure maximum level of emulsification of oils, surfactant mixtures and co-surfactant shown in Fig 4 - Ternary phase diagram .

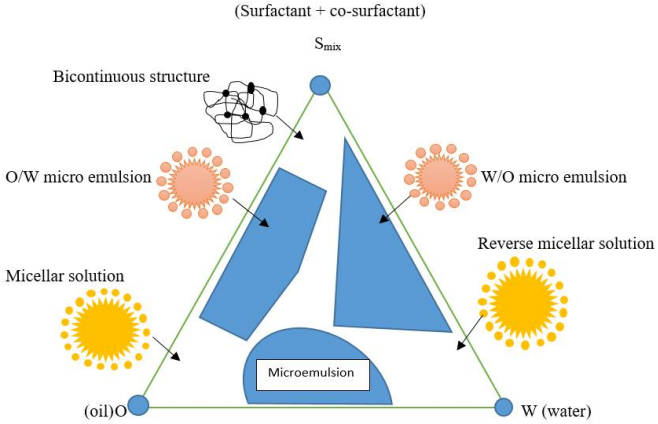

Fig 4: Ternary phase diagram

The upper part triangle acts as a ternary phase diagram of surfactant, co-surfactant & oil. In specific dilution and water titration processes are used to plan the phase drawing [28]. Phase diagram used to control micro emulsion regions. [6] For each compound, the percentage of oil, surfactants, and co-surfactants was 100%. Globule size, transmittance & separation of phase of micro emulsion formed were measured [29].

- **Dilution Process**

Ternary mixtures flexible compounds of surfactant, co-surfactant & oil can be required. Concentration of the surfactant varies from 30-75% (w / w), Concentration of oil varies from 25-75percent and the concentration of the co-surfactant varies from 0-30%. The amount of Smix concentrate and oil concentrate is added 100% to the whole mixture [30].

- **Water titration method**

By titration of homogeneous liquid mixtures of oil, Smix with water at room temperature, the phase diagram is obtained. Oil &Smix (surfactant: co-surfactant ratio) is prepared at a ratio of 9: 1 to 1: 9 and is measured into screw-cap glass tubes and vortexes. Then slowly squeeze the whole mixture with distilled water and stir at room temperature to obtain a uniform consistency. Once the consistency is arrived, mixture is again titrated in distilled water till transparency available. The sample is clearly and isotropically located to be in the micro-emulsion region. According to findings, the appropriate % of oil, co-surfactant &surfactant is picked, attached to the phase diagram and used for SMEDDS structural adjustments.[31]

Methods used to produce solid SMEDDS

• **Spray drying:** In a suitable solvent, SMEDDS liquid and solid carrier are combined.. Solvent became an atomic spray for fine droplets [32].

• **Adsorption into rigid carriers:** Liquids are attracted to free-flowing powders which have a very high surface area and tend to adsorb a large amount of oily substances. The adsorbents have a SEDDS / SMEDDS adsorbing fluid information of up to 70% of their weight. The ranges of Neusilin FL2 and Neusilin UFL 2, and Florite R is transferred to have a good oil adsorbing capability. The Compressibility index (CI) of Florite R is not good, while it has excellent flowing properties. Therefore, Florite R may be a suitable adsorbent for filling capsules. Although, because of low compressibility index, it is not selected to compress into a form of oral dose. Neusilin FL2, however, is an appropriate adsorbent for filling capsule and oral form because it has a good flow rate, increased oil adsorbing capability, and higher Cl [33].

• **Melt granulation:** Granular lubrication offers several advantages over traditional wet granulation for one-step operations because aqueous filling is no longer necessary as the final stage in drying [34].

• **Spheronization by extrusion:** After mixing SMEDDS liquid with the extrusion aid, water is added until the mast is sufficiently moist for extrusion. This became spheronized to form similar pellets. Pellets are dried and size-separated.. Various techniques used to modify strong SMEDDS showing high lipid exposure and high drug loading i.e Capsule Filling, Spray Drying, Adsorption on solid carrier, Melt Granulation, Melt Extrusion.

PHYSICO-CHEMICAL PROPERTIES OF SMEDDS

- **Formulation/ Composition of SMEDDS**

The reason for this application is that it produces oil in water (o / w) micro emulsion in light movement thenpurification by liquid phases. The composition usually consists of drugs, oil-containing substances, surfactant, co-surfactants and co-solvents.[1] This automatic form of emulsion compacted within the digestive tract reflects drug in a highly soluble form gives a concentrated compound for absorption of drug [35].

- **Drug selection for SMEDDS**

It is essential to understand that an interesting drug may have a major effect on different aspects of SMEDDS, like phase behaviour & droplet size of microemulsion. Several scientific chemical effects, like logP, molecular structure, pKa & weight, availability of ionisable groups & amount have a major impact on SMEDDS ability. Low-dose drug therapies are eligible type for SMEDDS [36]. The first hurdle in developing oral contraceptives was maintaining the drug's solubility in the gastrointestinal tract and, in particular, increasing the solubility in the large intestinal absorption.[37]

- **Choice of Excipients for SMEDDS**

In order to build an effective SMEDDS for optimum pharmacological effects, therefore it should be accompanied by given factors:

- Physicochemical properties of drug also excipients.
- Capability of drug interaction.

- Physiological component that promote or inhibit bioavailability.
- Temperature at which the emulsification takes place.

BIOPHARMACEUTICAL SYMPTOMS

- Potency of lipids and foods that increase the bioavailability of water-soluble drugs is throughout reviewed. Variation (reduction) in bowel movement
- Lipids may increase bioavailability by numerous possible mechanisms, which inturn may reduce delivery to absorption site & improve available time spent.

Existence of lipids within digestive tract promotes rise in secretion of bile salts (BS) & endogenous biliary lipids as well as phospholipids (PL) & cholesterol (CH), which are key to preparation of BS / PL mixed micelles / CH & an increase in intensification capability of alimentary tract.[38] The interaction of regulated lipids in these baccalaureate structures directly or in the digestive tract, causes inflammation of micellar structures & a further rise in dissolving capability[39].

- **Stimulation of intestinal lymphatic transport**

With excessive lyophilic therapy, lipids can enhance lymphatic transport of intestines & increase availability of bioavailability by reducing the body's first pass metabolism.[40]

- **Modifications in the biochemical function of the digestive tract**

The p-glycoprotein flow pump demonstrates that some lipids and surfactants can lessen the impact of enteric flow channels and reduce the pace of enterocyte-based metabolism.[41]

- **Other physical activity of the GI tract**

Certain mixtures of lipids have increasing penetration properties. In first case, however, passive enteric porosity not considered as a serious obstacle to the bioavailability of a mass of drug that does not dissolve and, in specific, lipotropic [42].

CHARACTERIZATION OF SMEDDS

SMEDDS can be estimated as follows.

- **Dispersibility test**

Self-emulsification capacity is tested using Std. USP XXII pairs per millilitre per compound added to 500 ml of 37 ± 0.5˚C water. In vitro performance of correction is tested for mistreatment of below system of grading: [43]

Grade A: Form a nanoemulsion quickly, which appears transparent or blue.
Grade B: Forms a fast, gradual emulsion that appears slowly.
Grade C: Good white emulsion in a few minutes.
Grade D: A slightly oily white emulsion takes time to form (more than 2 minutes).
Grade E: Composition, that results in minor emulsification with large droplets of oil present.

Formation of Grade A and Grade B is a nano emulsion when dissolved in GIT, but the formation of Grade C may be advised in the formation of SMEDDS.

- **Turbidimetric testing**

The nepheloturbidimetric analysis was completed to determine the emulsification increase. The maximum amount of the exhaust system is compared with maximum amount of 0.1M HCl on continuous vibration (50revolutions / min) in the magnetic stirrer at room temperature & increase in turbidity is measured using turbidimeter [44].

- **Determination of viscosity**

Measured using a Brookfield viscometer. Viscosity confirms that system is a w / o or o / w type. If the system had a low viscosity it was an o / w type or vice versa [45].

- **Globule size analysis and particle size measurement**

gauge boson correlation chemical analysis (which analyses lightweight fluctuations due to Brownian particle movement)is used to measure globule size of emulsion. Diameter of the nanometric size of the globe is maintained after water purification 100 times which shows the compatibility of most systems with water.[47]

- **Transmission percentage and refractive index**

Percentage transfer, refractive index confirms transparency and stability of formulation on dilution. Dye occurs on dilution because of synthetic oil and polysorbate derivatives. The clarity decreases with the increase in the size of the oil globe. Refractometer is used to measure the refractive index. The data show that transfers> 90% are obviously natural [48].

- **Electroconductivity testing**

This method is useful to determine the type of emulsion to be either w/o or o/w type. SMEDDS system has ionic or non-ionic surfactant, water & oil. Therefore, the test is used to measure electro conductive nature of a system due to presence of non-ionic surfactants measured with an electro conductometer [49].

- **Thermodynamic stability studies**

Physiological stability of lipid-based formulation is even more important in its function, that may get negatively affected due to the precipitation of a drug. Weakened immune system leads to partial. Excipient separation that affects the performance and the visual appearance of the formulation. Although, the inconsistency between the composition and consequently the shell of the gelatine capsules leads to cracking or damage, delayed dispersion or inadequate drug release [50].

• Centrifugation

The authorized formulation of thawing cycles at all temperatures between 21°C to 25°C was completed at 3500 rpm for 30 minutes. That framed methods with no partial separation are used for freeze-thaw pressure tests [52].

• Freezing cycle

Those structures that have gone through this process show good stability without segmentation, cream or cracking.

- **Zeta potential measurement**

Zeta sizer is used to measure the zeta potential of microemulsion. Samples are put into pure zeta disposable cells and recorded the results [53]. By introducing new sample, cuvettes were washed with methanol & rinsed with a sample to be weighed before each test [54].

- **Bioavailability study**

Plasma profiles are determined in experimental animals after oral administration. Cmax and Tmax are calculated for oral administration.[55] The area below concentration-time curve was determined using a trapezoidal method. The related bioavailability of the tablet is calculated using the formula below. [56]

Relative Bioavailability (%) = (AUC test / AUC reference) x (Volume reference / Test dose)

The dialysis bag method and USP dissolution apparatus paddle type can be used along. It contains GI liquid 500ml used as dissolution medium at 37˚C and 100 rpm paddle speed [57]. Before observing, the dialysis bag is stored for 2 hours in 3ml blank medium. Later, the SMEDD correction is added to the release area, then the bag is removed at 30, 60, 120, 180 &240 min and concentration of drug was observed. After 2 hours, Median pH is converted to 6.8 with the introduction of trisodium phosphate [58]. This could be obtained from mice using a pH 6.8 both as a dissolution medium [59]. Divisor must be regularly collected and reassembled with a dissolution medium. Divisor, filtering with filtered paper and then analyse using spectrophotometer for drug content determination.

***In vivo* study**

Advanced SMEDDS can be tested on animal models in mice, rabbits or dogs. Pure drug, drug suspension and finished products were given to animal group and therefore for the content of drug analysis plasma HPLC method is used. Parameters like Cmax & AUC are calculated individually and compared the marketed product of the drug [60].

CONCLUSION

Lipid-based drug delivery systems, particularly SMEDDS, are trusted way to improve the bioavailability of soluble drug, as long as the drug must be strong for greater lipid solubility. That is why this review focuses on physicochemical &biopharmaceutical properties of SMEDDS, that can be beneficial in developing this method for obtaining a safe, stable and highly effective SMEDDS formulations.

This procedure is suitable for lipophilic drugs, which provide levels of rapid elimination, absorption and avoidance of the effect of early pre-systemic passage, enzymatic degeneration and stomach upset. This technology is suitable for drugs of the BCS class especially phase II, phase IV. Current research will draw notice to understanding role of each lipid. This review highlighted the developmental steps (solubility studies, pseudo ternary phase formation and various evaluation tests) needed to obtain a robust and stable dosage form.

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