INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Paper

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

Nagaveni Pommala*[1], Pranuth Atthoti[2], Swetha Meeniga[3], Mounika Gandham[4], Saravanakumar kasimedu[5]

[1,2,3,4,] *S V U College of Pharmaceutical Sciences, Sri Venkateswara University, Tirupati-517502, Andra Pradesh, India*
[5]*Seven Hills College of Pharmacy*

ARTICLE INFO

Published: 13 Jan. 2025
Keywords:
SMEDDS, Solubility, Oral bioavailability, Novel medication, Microemulsion, Formulation, Self-micro emulsion, Low solubility
DOI:
10.5281/zenodo.14638364

ABSTRACT

Nearly 40% of novel drug candidates demonstrate limited solubility in water, which is a difficulty in development of optimum oral solid dosage form in terms of formulation design and bioavailability of new pharmaceutical products. Many ways have been attempted to overcome these challenges either by means of changing the solubility or preserving the medicine in dissolved form beyond stomach transit time. These issues by altering the drug's solubility or keeping it liquid throughout the duration of the gastrointestinal transit. Lipid solutions, emulsions, and emulsion pre-concentrates have received a lot of interest because they may be made into physically stable formulations that are appropriate for encapsulating medications that are so poorly soluble. Due to their physical stability, ease of manufacturing, ability to be filled in soft gelatin capsules, and ability to produce a drug-containing micro-emulsion with a large surface area upon dispersion in the gastrointestinal tract, self-micro emulsifying drug delivery systems (SMEDDS) in particular have recently drawn increased attention. Through the intestinal lymphatic channel and drug partitioning into the aqueous phase of intestinal fluids, the emulsions will further aid in the medication's absorption. An overview of SMEDDS, a crucial technique for creating lipophilic medications, and several variables that may have an impact on the oral bioavailability of these medications are provided in this paper.

INTRODUCTION

The number of poorly water-soluble drug candidate compounds has steadily increased due to modern drug discovery methodologies; at present approximately 50% of newly discovered pharmacologically active chemical entities are

***Corresponding Author:** Nagaveni Pommala
Address: *S V U College of Pharmaceutical Sciences, Sri Venkateswara University, Tirupati-517502, Andra Pradesh, India.*
Email ✉: nagavenipatp@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

lipophilic and have poor water solubility. SMEDDS are a type of emulsion that has drawn special interest as a way to improve the oral bioavailability of medications that are not well absorbed. These systems are basically mixtures of oil and surfactant, or co-surfactants, which require less energy to form an emulsion when mixed with water. Natural or manufactured oils, cosurfactants, and surfactants possess the special capacity to produce fine oil-in-water (o/w) micro emulsions when mildly stirred and then diluted in aqueous media, including gastrointestinal fluids. SMEDDS create translucent micro emulsions with droplet sizes smaller than 500 nm, whereas droplets between 300 and 500 nm are formed by SMEDDS. The pace and amount of absorption may be improved by lipophilic pharmacological molecules with dissolution rate-limited absorption, which could lead to more repeatable blood-time profiles.[1] Several strategies are employed to improve the oral bioavailability of low water soluble medicines.[2]

The oral route has been the primary drug administration method for the long-term management of numerous illnesses due to its high level of patient compliance. The high lipophilicity of the drug itself, however, makes it difficult to administer 50% of the drug molecules orally. When it comes to formulation design and the bioavailability of new pharmaceutical products, over 40% of new medication candidates have poor water solubility, which makes it difficult to develop the best oral solid dosage form. To address these issues, numerous approaches have been employed, such as altering the drug's solubility or keeping it liquid during the stomach transit period.[3,4] The presence of surfactants in self-emulsifying formulations causes the resulting emulsion to increase membrane permeability, whereas medium and long chain oils improve lymphatic absorption (also known as lymphatic transport). These elements could have a major role in the formulations improved performance. [5,6,7,8] SMEDDS have gained popularity due to their stability, ease of manufacture, and ability to create a drug-containing micro-emulsion with a large surface area when dispersed in the gastrointestinal tract. Due to a quicker breakdown by gastrointestinal enzymes, the medication will either be transferred to mixed micelles or may be absorbed straight from the emulsion particle by partitioning into the aqueous phase of intestinal fluids. This will further improve the absorption of the drug.[9]

Physico-Chemical Aspects of SMEDDS

Formulation/Composition of SMEDDS

Drug, oily vehicle, surfactant, co-surfactant, and even co-solvents are typically included in the formulation. The fundamental idea behind this system is its capacity to create fine oil-in-water (o/w) micro-emulsions with mild stirring after being diluted by aqueous phases; in other words, the stomach and intestines digestive motility provides the agitation needed for self-emulsification in vivo in the gut lumen.[10]The medication is presented in a solubilized state by this spontaneous emulsion formation in the gastrointestinal tract, and the small size of the produced droplet offers a wide interfacial surface area for drug absorption. In addition to solubilization, the inclusion of fat in the formulation influences medication absorption, which enhances bioavailability.[11,12]

Selection of Drug for SMEDDS

It is crucial to understand that the drug of interest may also significantly affect the different SMEDDS characteristics, including phase behaviour and micro-emulsion droplet size. SMEDDS performance is significantly impacted by a number of the drug's physicochemical characteristics, including pKa, log P, molecular weight, structure, quantity, and presence of ionizable groups. The best medication candidates

for SMEDDS are those with modest therapeutic doses.[13] Maintaining medication solubility in the GIT and more specifically optimizing drug solubility in the gut's prime absorptive site is one of the fundamental issues in the design of oral formulations.[14] Accessible for SMEDDS unless they exhibit good solubility in at least one of the SMEDDS excipients, ideally the lipophillic phase. Throughout the SMEDDS formulation's shelf life, the drug release pattern must not change and the drug must be chemically and physically stable in the formulation. As shown in Table 1, these systems can assist in resolving the issues listed below for each of the BCS class medication categories.[15]

Table 1: Applications of SMEDDS in various BCS class drugs

BCS class	Aqueous solubility	Membrane permeability	Problems
Class I	High	High	Gut wall efflux, enzymatic degrdation
Class II	Low	High	Solubilization and bioavailability
Class III	High	Low	Enzymatic degradation, bioavailability and gut wall efflux
Class IV	Low	Low	Bioavailability, enzymatic degradation, gut wall efflux, solubilization

Selection of excipients for SMEDDS

The USFDA's list of "GRAS" excipients, or generally recognized as safe, should be used to select the excipients. For formulation development to be effective, a thorough understanding of excipient properties and how they function in formulations is essential. To create an effective SMEDDS with the greatest possible therapeutic impact, The following elements need to be properly taken into account;

- The drug's physicochemical characteristics and excipients
- Possible interaction between drug excipients
- physiological elements that can increase or decrease bioavailability
- biopharmaceutical characteristics, such as the excipients' physical state at room temperature, solubility, regulatory status, and miscibility.
- Aspects of excipient regulation
- The point at which self-emulsification takes place

Formulation development typically begins with the selection of excipients because medications must be put into a suitable mixture of excipients when creating SMEDDS. To save time and money, certain generic criteria for selecting excipients were established because there are numerous lipid-based compounds that can be employed to formulate SMEDDS. Because of their safety, drug solubility and stability in excipients, and other attributes, a small number of excipients are identified during preliminary selection studies as potentially suitable for additional investigation. As important as having enough solubilization capacity for the medicine to be included is the initial selection of prospective excipients, which is followed by the creation of phase diagrams to determine appropriate mixing ratios for homogeneous formulations. To forecast the drug's fate in the GIT, potential formulations are put through in vitro dispersion and digesting studies on the drug-loaded systems.[15,16]

Oil/lipid phase

To enhance medication loading and the hydrophobic active moiety's bioavailability, the oil phase in a self-micro emulsifying system solubilizes the hydrophobic/lipophilic active moiety. According to Small's Lipid Classification scheme, the lipid portion of the SMEDDS, which makes up the core of the emulsion particle, is usually made up of nonpolar or Class I polar

lipids.[17] Excipient vendors offer a large variety of lipid excipients. The properties of different excipients must be understood because these lipids have an impact on the absorption process. To increase the amount of medicine that may be dissolved, a lipid molecule with a large hydrophobic region relative to a hydrophilic section is preferred. Triglyceride vegetable oils are the most often utilized excipients in lipid-based medication delivery. Due to their complete digestion and absorption, this particular family of lipids poses no safety risks. LCT, MCT, and SCT are additional classifications for triglycerides. The effective concentration of ester groups mostly determines a drug's solvent capacity.[18]

Surfactants

In addition to the oily drug carrier vehicle, the formulation must contain comparatively significant amounts of surfactant due to the self-emulsifying capabilities. The intestinal membrane's permeability may be increased or the binding between lipids and the membrane may be enhanced by the surfactants. By dividing into the cell membrane and upsetting the lipid bilayer's structural arrangement, surfactants increase permeability and improve penetration.[19] As a result, the majority of medications are absorbed passively through the cell. Additionally, they increase the drug's rate of disintegration to further enhance absorption. SMEDDS formulation requires careful consideration of surfactant choices. When selecting a surfactant for SMEDDS formulation, it's important to consider its HLB value and safety. The HLB of a surfactant provides important information for its use in SMEDDS formulation. To achieve good self-emulsifying performance, the surfactant/emulsifier used in SMEDDS formulations should have a high HLB and hydrophilicity, allowing for rapid dispersion in aqueous GI fluid as a fine oil-in-water emulsion.[20]

Acrosyl, a castor oil derivative, has been shown to provide optimal self-emulsification.[21] Nonionic surfactants are chosen over ionic surfactants for their decreased toxicity and improved emulsion stability throughout a wider pH and ionic strength range. However, they may have a reversible effect on intestinal permeability, which could be a drawback[19]. This improves absorption of the co-administered medication. Hydrophobic surfactants can penetrate membranes, altering fluidity and permeability. One important consideration when selecting a surfactant is safety. Natural emulsifiers, such as lecithin, alkaline medium chain monoglycerides (MCM) and peceol, are typically chosen since they are thought to be less harmful than synthetic surfactants. Nevertheless, the self-emulsification efficiency of these excipients is limited.[22] Bulky surfactants, including polysorbates and triglyceride ethoxylates, are less harmful because single alkyl chains penetrate more deeply. To achieve stable SMEDDS, surfactant concentrations typically range from 30 to 60% of the total formulation.[23]

Co-surfactants/Co-solvents

High surfactant concentrations (up to 50%) are typically needed for the formulation of a good SMEDDS, and the addition of co-surfactants facilitates self-emulsification. Co-surfactant with an HLB value of 10–14 is typically employed with surfactant to improve drug loading to SMEDDS, fluidize the hydrocarbon portion of the interfacial layer, reduce oil-water interfacial tension, and permit the spontaneous production of microemulsion.[24] For this reason, amphiphilic solubilizers and/or hydrophilic or lipophilic surfactants are employed. When co-emulsifiers or solubilizers are introduced into SMEDDS, phase diagrams may reveal a rising self-micro-emulsification zone. Large amounts of the medicine or the hydrophilic surfactant can be dissolved in the lipid phase using organic solvents such ethanol, PEG and PG. which are appropriate

co-solvents for oral administration. SMEDDS develops in lipid mixtures with higher surfactant and co-surfactant:oil ratios.[25]

Mechanism of Self-Emulsification

When the energy needed to expand the dispersion's surface area is less than the entropy change favoring dispersion, self-emulsification takes place. The energy needed to form a new surface between the water and oil phases directly determines the free energy of the typical emulsion, which is defined by the formula:

$\Delta G = \sum Ni\ \pi ri\ 2\ S$

where N is the number of droplets of radius r, S is the interfacial energy, and ΔG is the process's free energy (not including the free energy of mixing). Emulsifying agents stabilize the emulsion by forming a monolayer of emulsion droplets, which lowers the interfacial energy and acts as a barrier to prevent coalescence. Over time, the two phases of the emulsion tend to separate to reduce the interfacial area.[26,27] Pouton has suggested a connection between the system's phase inversion behavior and the surfactant's emulsification characteristics. For instance, when the temperature of the oil-in-water system is raised and stabilized with one or more non-ionic surfactants, the surfactant's cloud point is reached and phase inversion occurs. Since the surfactant is very mobile at the temperature of phase inversion, the o/w interfacial energy is reduced, which lowers the energy required for emulsification.

Characterizations of SMEDDS

SMEDDS can be characterized in numerous ways, as listed below;

1. Visual Assessment

Visual evaluation is the main method of self-emulsification assessment. Important details regarding the mixture's self-emulsifying and micro-emulsifying properties as well as the resulting dispersion may be revealed by this.

2. Equilibrium Phase Diagram

Equation phase diagrams allow for the comparison of various surfactants and their interactions with co-solvents. Visual evaluation of a phase region's borders is simple. A ternary phase diagram can be used to illustrate the phase behavior of a three-component system. Phase diagrams aid in figuring out the ideal concentrations of various excipients required to achieve drug loading, self-emulsifying ability, and homogeneous pre-concentrates. When more than three components are employed, those that are closely linked are joined together as one component and handled as such in the diagram. Each corner of the phase diagram indicates 100% of the specific components.[28]

3. Turbidity Measurement

By determining whether the dispersion approaches equilibrium quickly and in a repeatable amount of time, this assesses the effectiveness of self-emulsification.[29] Turbidity meters (the Orbeco-Helle turbidity meter and the Hach turbidity meter) are used for these measurements.[30]

4. **Droplet Size**

To determine the emulsion's droplet size, a Coulter Nanosizer, photon correlation spectroscopy, or microscopic techniques are usually used.Since it affects the stability of the microemulsion and the pace and amount of drug release, droplet size plays a crucial role in self-emulsification performance.[31]

5. Electron Microscopic Study

Freeze-fracture electron microscopy is used to examine the surface properties of microemulsions.[32]

6. Zeta Potential Measurement

It is employed to determine the droplets charge.

7. Determination of Emulsification Time

This procedure is used to estimate how long emulsification will take. Using a revolving paddle to encourage emulsification in a crude nephelometer, the effectiveness of emulsifying different surfactant and lipid compositions is measured.[33]

8. Particle Size Distribution

The microemulsion's particle size distribution is measured using dynamic light scattering methods. This measures the velocity of the Brownian diffusion and, in turn, the dispersed droplets using the variation in scattered light intensity. Cryogenic transmission electron microscopy (cryoTEM) may be used to confirm particle size distributions in more detail. [34]

9. Conductivity Measurement

The point at which the system transitions from an oil continuous phase to a water continuous phase may be found using conductivity measurements. Additionally, it facilitates the observation of percolation or phase inversion occurrences.[35]

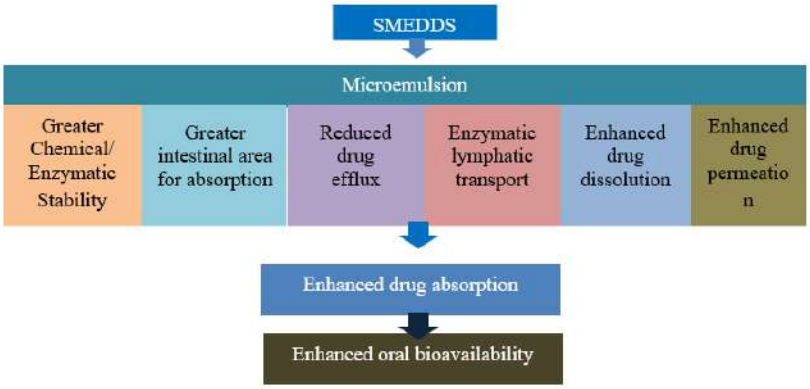

Figure 1: Key elements that could influence the bioavailability of medications made with SMEDDS

Biopharmaceutical Aspects of SMEDDS

By speeding up the dissolution process, reducing particle size to the molecular level to facilitate the formation of solubilized phases, producing a solid state solution inside the carrier, modifying drug uptake, efflux, and disposition by altering enterocyte-based transport, and improving drug transport to the systemic circulation via the intestinal lymphatic system, these systems increase absorption from the gastrointestinal tract.[36,37,38]

- **Effect of Lipids**

Because lipids can change the drug's biopharmaceutical properties through a variety of methods, their impact on the bioavailability of medications taken orally is quite complicated. The volume of lipid given the degree of saturation and the length of the triglyceride's acid chain can all have an impact on the drug's absorption profile and blood/lymph distribution.

- **Effect on Rate of Gastric Emptying**

An increase in stomach residence time indicates that the medication is being delivered to its site of action. Specifically, the food's lipid content is essential for the absorption of lipophilic medications. The GI tract's lipids cause a delay in the emptying of the stomach, which lengthens the gastric transit time and increases the oral bioavailability of the lipophilic medication.[39]

This can be explained by a high-fat meal's capacity to enhance intestinal wall permeability, decrease metabolism and efflux activity, promote biliary and pancreatic secretions, lengthen GIT residence duration, and facilitate lymphatic system transfer. Long-chain fatty acids and triglycerides are important factors in extending the GIT residence duration.[40]

- **Effect on Digestion and Solubilization of Drug**

The pace and degree of absorption of a medicine are determined by the equilibrium between its solubility in the gastrointestinal lumen's aqueous environment and its penetration through the lipophilic membrane of enterocytes.[41]

Gastric lipase starts the digestion of exogenous dietary triglycerides(TG) and formulation TG once SMEDDS are consumed. At the same time, a crude emulsion is formed by the stomach's mechanical mixing (propulsion, grinding, and retropulsion). Pancreatic lipase and its cofactor co-lipase finish breaking down TG into diglycerides, monoglycerides, and fatty acids later in the small intestine. Pancreatic lipase mostly produces 2-monoglycerides and free fatty acids at the sn-1 and sn-3 sites of TG. [42,43] Pancreatic phospholipase hydrolyzes a single fatty acid molecule from the sn-2 position of formulation or biliary-derived phospholipid (PL) in the small intestine, producing lysophosphatidylcholine and fatty acid as a byproduct of this chemical digestion.[44]

Endogenous biliary lipids, such as cholesterol, PL, and bile salt (BS), are secreted from the gallbladder in response to the presence of exogenous lipids in the small intestine. In the presence of bile salts, previously generated monoglycerides, fatty acids, and lysophospholipid products of lipid digestion subsequently combine to create a variety of colloidal structures, such as micelles and unilamellar and multilamellar vesicles. These produced lipid metabolites greatly improve the small intestine's solubility and absorptive ability for lipid digestion products and medications Mixed micelles and micro-emulsions are absorbed by pinocytosis diffusion or endocytosis after passing through the mucin and aqueous layer. The medication molecule then travels through the lymphatic or portal veins to enter the systemic circulation.[45]

- **Effect on intestinal permeability**

By entering the hydrophobic region of the surfactant monolayer, the oil component modifies the drug's solubility in SMEDDS. The molecular volume, polarity, size, and shape of the oil molecule all affect how much oil penetrates a surface. The solubility of the medication in SMEDDS as a whole is always greater than that of the drug in the separate excipients that make up SMEDDS. However, the drug's solubility in the oil phase, its interfacial location, and interactions between the drug and surfactant at the interface all play a significant role in this increased solubility.[46] Light scattering investigations revealed that oils with tiny molecular volumes work as co-surfactants, penetrating the surfactant monolayer. The formation of thin polyoxyethylene chains near the micelle's hydrophobic center disrupts drug solubility, resulting in lower solubility. However, oils with a large molecular volume create a separate core and are unable to efficiently permeate the surfactant monolayer. It was discovered that the drug's microstructure and solubility in the excipients had an impact on the locus of drug solubilization. For phytosterols, the site of drug solubilization was shown to be at the micelle interface but for cholesterol, it was discovered to be situated between the hydrophobic head groups of surfactant molecules. Compared to cholesterol, this is explained by the extra substitution of an alkyl side chain, which changes the side chain flexibility of phytosterol.[47] Drug solubility in oil is influenced by the physicochemical characteristics of the drug molecule itself in addition to the oil's polarity and molecular volume. Only in the early phases of screening may Lipinski's rule of five and the BCS classification be taken into account when choosing a medication. Despite having acceptable absorption and disposition, several acidic medicines are classified as Class II according to the BCS because they do not meet the criteria of greater solubility at low pH levels. Conversely Lipinski's rule of five only applies when the medication is not an active transporter substrate. This implies that log P and aqueous solubility by themselves are insufficient to forecast a drug's solubility in oil. This further suggests that any two medications with comparable log P would not

have the same solubility because of their dissimilar physicochemical characteristics.[48]

Effect of surfactants

- **Effects on permeability**

By disrupting the lipid bilayer of the single layer of the epithelial cell membrane, surfactants enhance permeability.[49] The rate-limiting barrier to drug absorption and diffusion is formed by the single layer of the epithelial cell membrane and the undisturbed aqueous layer.[50] As a result, the passive transcellular route is how most medications are absorbed. Surfactants promote penetration by partitioning into the cell membrane and upsetting the lipid bilayer's structural arrangement. Additionally, they improve absorption by speeding up the drug's rate of disintegration.[51] Additionally, they improve absorption by speeding up the drug's rate of disintegration.[52]

- **Effect on Droplets Size**

SMEDDS are formed by lipid mixtures with greater ratios of surfactant and cosurfactant to oil.[53] Between 30% and 60% (m/m) of surfactant is needed to create a stable SMEDDS.[54]

To avoid irritating the stomach, the lowest surfactant content is recommended. In the case of SMEDDS, the incredibly small droplet size generated encourages quick stomach emptying and low local surfactant concentration, which lessens gastrointestinal discomfort. There is a correlation between the droplet size and the surfactant concentration being used. It has been demonstrated that the concentration of surfactant affects the emulsion's droplet size differently. Although the opposite is conceivable because of increased water penetration into oil droplets, which results in their dissolution, an increase in surfactant concentration produces a decrease in droplet size connected to surfactant molecules' stability at the oil-water contact.[19]

In some situations, such as when a combination of saturated C8-C10 polyglycolized glycerides (Labrafac CM-10) is present, raising the surfactant concentration may result in droplets with a lower mean droplet size. The stability of the oil droplets due to the surfactant molecules' localization at the oil-water interface may help to explain this.[55] However, in certain instances, when surfactant concentrations rise, the mean droplet size may also rise. This phenomena may be explained by the ejection of oil droplets into the aqueous phase as a result of the interfacial disruption caused by greater water penetration into the oil droplets mediated by the increased surfactant concentration. Surfactants in SMEDDS reduce interfacial tension and curvature, allowing for dispersion and the formation of a flexible film that covers the lipid core of emulsion droplets, resulting in a nano- or micro-emulsion. The water-oil contact lowers interfacial tension. Adding a second surfactant often reduces interfacial tension to a negligible level causing the surface to expand and create tiny droplets.[56]

CONCLUSION

The study explains how equilibrium phase diagrams and other measurement techniques aid in explaining the biopharmaceutical features of self-emulsifying drug delivery systems (SMEDDS). It also illustrates how the size of the droplets, the quantity of surfactants, and the ratio of lipids affect the drug's solubility, absorption, and ultimately its bioavailability in the gastrointestinal tract. Innovative formulation techniques like Self-Micro emulsifying Drug Delivery Systems (SMEDDS), which increase oral bioavailability by producing stable micro-emulsions that improve drug absorption in the gastrointestinal tract, are required due to the rising prevalence of poorly water-soluble drug candidates. SMEDDS may successfully handle the difficulties presented by lipophilic medications by carefully choosing excipients and refining formulation

characteristics, which will ultimately result in better therapeutic outcomes.

REFERENCES

1. Spernath A, Aserin A. Microemulsions as carriers for drugs and nutraceuticals. Advances in colloid and interface science. 2006 Dec 21;128:47-64.
2. Pande SV, Biyani KR. Microencapsulation by solvent evaporation method of BCS Class 4 drugs for bioavailability enhancement. Journal of Drug Delivery and Therapeutics. 2016 Sep 12;6(5):18-30.
3. Abdalla A, Klein S, Mäder K. A new self-emulsifying drug delivery system (SEDDS) for poorly soluble drugs: characterization, dissolution, in vitro digestion and incorporation into solid pellets. European journal of pharmaceutical sciences. 2008 Dec 18;35(5):457-464.
4. Pouton CW. Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. European journal of pharmaceutical sciences. 2006 Nov 1;29(3-4):278-287.
5. Charman WN, Stella VJ. Transport of lipophilic molecules by the intestinal lymphatic system. Advanced drug delivery reviews. 1991 Jul 1;7(1):1-4.
6. Porter CJ, Trevaskis NL, Charman WN. Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs. Nature reviews Drug discovery. 2007 Mar;6(3):231-248.
7. Sanghai B, Aggarwal G, HariKumar SL. Solid self microemulsifying drug deliviry system: a review. Journal of Drug Delivery and Therapeutics. 2013 May 13;3(3):168-174.
8. Dhakar RC, Maurya SD, Saluja V. From formulation variables to drug entrapment efficiency of microspheres: a technical review. Journal of Drug Delivery and Therapeutics. 2012 Nov 11;2(6).
9. de Smidt PC, Campanero MA, Trocóniz IF. Intestinal absorption of penclomedine from lipid vehicles in the conscious rat: contribution of emulsification versus digestibility. International journal of pharmaceutics. 2004 Feb 11;270(1-2):109-118.
10. Shah NH, Carvajal MT, Patel CI, Infeld MH, Malick AW. Self-emulsifying drug delivery systems (SEDDS) with polyglycolyzed glycerides for improving in vitro dissolution and oral absorption of lipophilic drugs. International journal of pharmaceutics. 1994 May 16;106(1):15-23.
11. Charman SA, Charman WN, Rogge MC, Wilson TD, Dutko FJ, Pouton CW. Self-emulsifying drug delivery systems: formulation and biopharmaceutic evaluation of an investigational lipophilic compound. Pharmaceutical research. 1992 Jan;9:87-93.
12. Pouton CW. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying'drug delivery systems. European journal of pharmaceutical sciences. 2000 Oct 1;11:S93-98.
13. Singh B, Bandopadhyay S, Kapil R, Singh R, Katare OP. Self-emulsifying drug delivery systems (SEDDS): formulation development, characterization, and applications. Critical Reviews™ in Therapeutic Drug Carrier Systems. 2009;26(5).
14. O'driscoll CM, Griffin BT. Biopharmaceutical challenges associated with drugs with low aqueous solubility—the potential impact of lipid-based formulations. Advanced drug delivery reviews. 2008 Mar 17;60(6):617-624.
15. Kohli K, Chopra S, Dhar D, Arora S, Khar RK. Self-emulsifying drug delivery systems:

an approach to enhance oral bioavailability. Drug discovery today. 2010 Nov 1;15(21-22):958-965.
16. Pouton CW. Formulation of poorly water-soluble drugs for oral administration. Bulletin Technique Gattefossé. 2005;98:39-51.
17. Small DM. A classification of biologic lipids based upon their interaction in aqueous systems. Journal of the American Oil Chemists Society. 1968 Mar;45(3):108-119.
18. Cao Y, Marra M, Anderson BD. Predictive relationships for the effects of triglyceride ester concentration and water uptake on solubility and partitioning of small molecules into lipid vehicles. Journal of pharmaceutical sciences. 2004 Nov 1;93(11):2768-2779.
19. Swenson ES, Milisen WB, Curatolo W. Intestinal permeability enhancement: efficacy, acute local toxicity, and reversibility. Pharmaceutical research. 1994 Aug;11:1132-1142.
20. Hauss DJ, "Oral lipid based Formulations-Enhancing the Bioavailablity of Poorly water soluble drugs," in Drugs and Pharmaceutical Sciences, 2007; 170:1–339,
21. Shah SR, Parikh RH, Chavda JR, Sheth NR. Self-nanoemulsifying drug delivery system of glimepiride: design, development, and optimization. PDA Journal of Pharmaceutical Science and Technology. 2013 May 1;67(3):201-213.
22. Constantinides PP. Lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects. Pharmaceutical research. 1995 Nov;12:1561-1572.
23. Pouton CW. Self-emulsifying drug delivery systems: assessment of the efficiency of emulsification. International journal of pharmaceutics. 1985 Dec 1;27(2-3):335-348.
24. Ozawa K, Olsson U, Kunieda H. Oil-induced structural change in nonionic microemulsions. Journal of dispersion science and technology. 2001 Feb 4;22(1):119-24.
25. Meinzer A. Microemulsion-A suitable galenical approach for the absorption enhancement of poorly soluble compounds. Bulletin Technique-Gattefosse. 1995:21-36.
26. Reiss H. Entropy-induced dispersion of bulk liquids. Journal of colloid and Interface Science. 1975 Oct 1;53(1):61-70.
27. Craig DQ, Barker SA, Banning D, Booth SW. An investigation into the mechanisms of self-emulsification using particle size analysis and low frequency dielectric spectroscopy. International journal of pharmaceutics. 1995 Jan 31;114(1):103-110.
28. Pouton CW, Wakerly MG, Meakin BJ. Self-emulsifying systems for oral delivery of drugs. InInternational Symposium on Control Release Bioactive Materials 1987 Jan 29 (Vol. 714, pp. 113-114).
29. Gursoy N, Garrigue JS, Razafindratsita A, Lambert G, Benita S, Bloom DR. Excipient effects on in vitro cytotoxicity of a novel paclitaxel self-emulsifying drug delivery system. Journal of Pharmaceutical Sciences. 2003 Dec 1;92(12):2411-2418.
30. Palamakula A, Khan MA. Evaluation of cytotoxicity of oils used in coenzyme Q10 Self-emulsifying Drug Delivery Systems (SEDDS). International Journal of Pharmaceutics. 2004 Apr 1;273(1-2):63-73.
31. Goddeeris C, Cuppo F, Reynaers H, Bouwman WG, Van den Mooter G. Light scattering measurements on microemulsions: estimation of droplet sizes. International journal of pharmaceutics. 2006 Apr 7;312(1-2):187-195.
32. Vyas SP, Khar RK. Submicron emulsion. Targeted and Controlled Drug Delivery Novel Carriers Systems. CBS Publishers and Distributors. 2002:291-294.

33. Pouton CW. Formulation of self-emulsifying drug delivery systems. Advanced drug delivery reviews. 1997 Apr 14;25(1):47-58.
34. Fatouros DG, Bergenstahl B, Mullertz A. Morphological observations on a lipid-based drug delivery system during in vitro digestion. European Journal of Pharmaceutical Sciences. 2007 Jun 1;31(2):85-94.
35. Greiner RW, Evans DF. Spontaneous formation of a water-continuous emulsion from aw/o microemulsion. Langmuir. 1990 Dec;6(12):1793-1796.
36. Humberstone AJ, Charman WN. Lipid-based vehicles for the oral delivery of poorly water soluble drugs. Advanced drug delivery reviews. 1997 Apr 14;25(1):103-128.
37. Kumar P, Kumar P, Kumar R, Kumar N, Kumar R. An overview on lipid based formulation for oral drug delivery. Drug Invention Today. 2010; 2:390–395.
38. O'Driscoll CM. Lipid-based formulations for intestinal lymphatic delivery. European Journal of Pharmaceutical Sciences. 2002 Jun 1;15(5):405-415.
39. Hunt JN, Knox MT. A relation between the chain length of fatty acids and the slowing of gastric emptying. The Journal of Physiology. 1968 Feb 1;194(2):327-336.
40. Wagner D, Spahn-Langguth H, Hanafy A, Koggel A, Langguth P. Intestinal drug efflux: formulation and food effects. Advanced drug delivery reviews. 2001 Oct 1;50:S13-31.
41. Pramod K, Peeyush K, Rajeev K, Nitish K, Rakesh K. An overview of lipid based formulation for oral drug delivery. Drug Inv Today 2010; 2:390–395.
42. Erlanson-Albertsson C. Pancreatic colipase. Structural and physiological aspects. Biochimica et Biophysica Acta (BBA)-Lipids and Lipid Metabolism. 1992 Apr 8;1125(1):1-7.
43. Borgström B. On the mechanism of pancreatic lipolysis of glycerides. Biochimica et biophysica acta. 1954 Jan 1;13:491-504.
44. Van den Bosch H, Postema NM, De Haas GH, Van Deenen LL. On the positional specificity of phospholipase A from pancreas. Biochimica et Biophysica Acta (BBA)-Lipids and Lipid Metabolism. 1965 Jun 1;98(3):657-659.
45. Kalepu S, Manthina M, Padavala V. Oral lipid-based drug delivery systems–an overview. Acta Pharmaceutica Sinica B. 2013 Dec 1;3(6):361-372.
46. Narang AS, Delmarre D, Gao D. Stable drug encapsulation in micelles and microemulsions. International journal of pharmaceutics. 2007 Dec 10;345(1-2):9-25.
47. Rane SS, Anderson BD. What determines drug solubility in lipid vehicles: is it predictable?. Advanced drug delivery reviews. 2008 Mar 17;60(6):638-656.
48. O'driscoll CM, Griffin BT. Biopharmaceutical challenges associated with drugs with low aqueous solubility—the potential impact of lipid-based formulations. Advanced drug delivery reviews. 2008 Mar 17;60(6):617-624.
49. . Swenson ES, Curatolo WJ. Means to enhance penetration. Adv Drug Del Rev 1992; 8:39–92.
50. Hauss DJ, Fogal SE, Ficorilli JV, Price CA, Roy T, Jayaraj AA, Keirns JJ. Lipid-based delivery systems for improving the bioavailability and lymphatic transport of a poorly water-soluble LTB4 inhibitor. Journal of pharmaceutical sciences. 1998 Feb 1;87(2):164-169.
51. Kim HJ, Yoon KA, Hahn M, Park ES, Chi SC. Preparation and in vitro evaluation of self-microemulsifying drug delivery systems containing idebenone. Drug development and

industrial pharmacy. 2000 Jan 1;26(5):523-529.
52. Asadujjaman MD, Mishuk AU. Novel approaches in lipid based drug delivery systems. Journal of Drug Delivery and Therapeutics. 2013 Jul 13;3(4):124-130.
53. Meinzer A. Microemulsion-A suitable galenical approach for the absorption enhancement of poorly soluble compounds. Bulletin Technique-Gattefosse. 1995:21-26.
54. Pouton WC. Properties and uses of common formulation lipids, surfactants and cosolvents. InAAPS, Workshop 2007 Mar 5.
55. Levy MY, Benita S. Drug release from submicronized o/w emulsion: a new in vitro kinetic evaluation model. International journal of pharmaceutics. 1990 Dec 1;66(1-3):29-37.
56. Kommuru T, Gurley B, Khan MA, Reddy IK. Self-emulsifying drug delivery systems (SEDDS) of coenzyme Q10: formulation development and bioavailability assessment. International journal of pharmaceutics. 2001 Jan 16;212(2):233-246.

HOW TO CITE: Nagaveni Pommala, Pranuth Atthoti, Swetha Meeniga, Mounika Gandham, Saravanakumar kasimedu, A Review on Physico-Chemical and Biopharmaceutical Aspects of Self-Micro Emulsifying Drug Delivery System (SMEDDS), Int. J. of Pharm. Sci., 2025, Vol 3, Issue 1, 994-1005. https://doi.org/10.5281/zenodo.14638364