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Review Article

Lipid Based Drug Delivery System : The Best Way For Better Absorption

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ABSTRACT

Above half of the new chemical entities are lipophilic in nature. The major problem in the oral formulation of BCS Class II and IV drugs is lower and inconsistent bioavailability, which is primarily resulted from poor water solubility and slow dissolution rate. It may lead to high intra and inter-subject variability and therapeutic failure. Lipid based formulations has gained more popularity with oils and the possess greater bioavailability because of their ability to bypass the passage into hepatic portal vein and evade hepatic degradation. Self-emulsifying drug delivery systems(SEDDS) is one of the formulation approaches of Lipid based formulations which plays a vital role in tackling these problems. It is an isotropic mixture of oils, surfactants, and co-surfactants. It emulsifies spontaneously in the gastrointestinal tract with the aid of GI fluids presenting the drug in the solubilized state and the small size of formed droplets provides a large interfacial surface area for better absorption through the lymphatic pathway, bypassing the first pass metabolism. These in-situ emulsifying systems have high stability even after incorporating various dosage forms. Recently, studies suggested that using SEDDS as a nanocarrier to enhance mucus permeability is frequently adopted because oral transport of peptides and proteins is prone to mucus barrier and mucosal enzymatic degradation. This article presents an in-depth review of SEDDS which may be a promising approach to successfully address the problems of drug molecules that are not radially soluble.

INTRODUCTION

Over 30% of drugs that are frequently marketed and almost half of new chemical entities received by formulation scientists do not have enough aqueous solubility which leads to low oral bioavailability (1,2). Since dissolution in the external lumen is the rate-controlling step for absorption hence, the oral bioavailability of

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numerous potent lipophilic drugs is low due to their limited water solubility (3). There are various formulation strategies exploited to overcome this problem, including the use of lipids, surfactants, micronization, salt formation, permeation enhancers, cyclodextrins, solid dispersions, and nanoparticles (4,5). Recently, Self-emulsifying drug delivery system (SEDDS), which is a lipid-based formulation has been getting lots of interest in effort to increase the oral bioavailability of lipophilic drugs. This system is an isotropic mixture of drugs, lipids, and surfactants, usually with one or more hydrophilic cosolvents or co-emulsifiers (4). Actually the lipids present in duodenum stimulates the release of Cholestrol and bile salts and form micelles.The hydrophilic part of the micelle is attracted to aqueous portion and lipophilic part will remain with core.Micellar solubilisation occurs when lipid formulation gets to duodenum and caues the drug to be entrapped in a colloidal micelle ,enhancing drug solubility. Pouton has developed a self-emulsifying drug delivery system for the first time using Miglyol 812 and Tween 85 to deliver poorly water-soluble drugs ultimately resulting in their improved solubility and bioavailability (6). This increased the interest of formulation scientists and researchers to step up their work on SEDDS. It holds the capability to solubilize the hydrophobic components and enclose them within a single unit dosage form for oral administration. The theory behind the enhancement of dissolution rate using SEDDS is, the emulsion forms instantly in the GI tract as the drug moiety comes in contact with it, supported by mild gastric mobility. Hence, the drugs in solubilized state are delivered. The micro/nano-emulsified drug avoids the hepatic first-pass metabolism and gets easily absorbed through the lymphatic system because of its small globule size which provides a large interfacial area (7). The development of formulations with the nanoscale particle size and narrow distribution has been considered to provide an excellent in-vivo performance, with the dispersion in GIT being critical aspect. Conversely, it has been claimed that the drug absorption was not affected by droplet size of emulsion (8). These are different from traditional oral drug delivery systems because the enzymatic digestion significantly alters the formulation excipients (9). Fig. 1 indicates how self-emulsification occurs and their mechanism of action

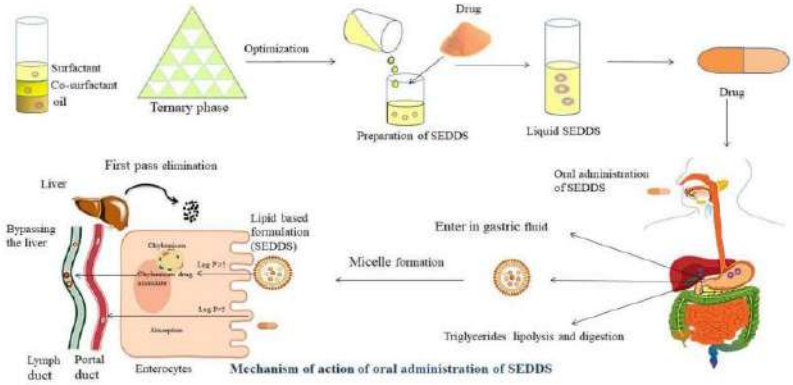

Fig 1: Process of self-emulsification and mechanism of action of SEDDS

Self-micro-emulsifying drug delivery system (SMEDDS) refers to the formulation that produce clear microemulsions with size of oil droplets as small as 100-250 nm. In past few years, the term self-nano-emulsifying drug delivery system (SNEDDS) has been used to refer the globule sizes smaller than 100 nm (10). Among the non-viral vectors, SNEDDSs are regarded as an innovative approach for oral gene delivery. Nucleic acids such as pDNA, siRNA, and microRNA could be added to nano-emulsion dispersion to prevent them from metabolic degradation by enzymes and

promote their cellular uptake. For the oral administration of hydrophilic macromolecules such as pDHA, peptides, proteins, hormones, enzymes and polysaccharides, SEDDS has also been developed. (11).

POTENTIAL ADVANTAGES OF SEDDS OVER CONVENTIONAL EMULSION (3,12–15).

1. **Easy to manufacture and scale up (Pilot – plant production) –**

Conventional emulsions require strong shear for producing a dispersion while preparation of SEDDS is basically dissolving the drug in oil with further addition of surfactant-cosurfactant mixture. For large scale production, they require relatively simple and affordable premises like an agitator mixture and volumetric liquid filling equipment. This explains why the pharmaceutical industries are interested in SEDDS.

2. **Enhancement in the oral bioavailability –**

When the orally administered drug reach to GI tract in a solubilized and/or micro-emulsified form, it is transported more efficiently through the absorptive brush border and intestinal membrane due to increase in their specific surface area. Fig. 2 demonstrate using SEDDS, how the bioavailability of poorly water-soluble drugs get enhanced.

3. **Consistent drug absorption profile –**

These formulations offer a significant interfacial area for drug partitioning between oil and water. Hence, there is more consistent temporal profile for better drug absorption and an exclusive drug targeting towards a particular GI tract absorption window.

4. **Physical stability –**

Being transparent, isotropic mixtures, and resistant to minimal temperature variations, these are physically stable and overcome the instabilities like creaming, breaking, and phase inversion after long-term storage. Conventional emulsions cannot be autoclaved because of phase inversion temperature, but SEDDS can be autoclaved.

5. **Reduction in dose –**

These are able to reduce the dosing frequency, which leads to more consistent absorption time profiles. It possesses predictable therapy due to less inter-subject and intra-subject variability.

6. **Protection of sensitive drugs –**

It prevents drugs from becoming hydrolyzed by GI enzymes as well as reduces the primary systemic clearance and hepatic first-pass metabolism within the GI mucosa due to their ability to load drugs in the inner phase.

7. **Versatility of dosage form –**

It has flexible dosage forms that can be applied to either liquids or solids. To improve patient satisfaction, this formulation can be placed in soft/hard gelatin capsules, which may be packed in blisters or strips if the dose is uniform throughout each capsule.

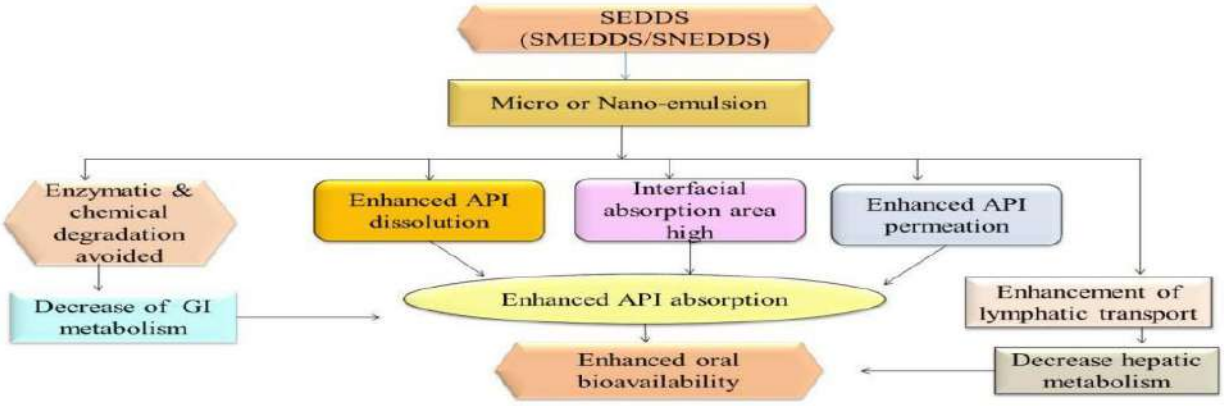

Fig 2: Bioavailability enhancement of orally administered poorly water-soluble drugs using SEDDS

DISADVATAGES OF SEDDS (13,14)

1. The surfactant concentration may increase the potential for instabilities of drug and cause gastric irritation.
2. During formulation there might be a variation in drug loading, which can affect dose frequency.
3. Sometimes, co-solvents can reside in the formulation and lead to the degradation of drugs.
4. On dilution, the tendency of the drug to precipitate is more because the hydrophilic solvents possess dilution effect.

LIMITATION OF SEDDS

Development of the SEDDS and other lipid-based formulations has been hindered due to the absence of suitable predictive in-vitro models for assessing them (16,17). Conventional dissolution methods are insufficient because these formulations eventually depend upon digestion before release of drug. An in-vitro model that simulates the digestive activity of duodenum has been developed in order to reflect this. Before the potency to be evaluated, this in-vitro model with several lipid-based prototypes are needed for further development and validation using a suitable animal model. The in vitro-in vivo correlations will serve as the foundation for future development of SEDDS. (1,18).

MECHANISM OF SEDDS

Every aspect of the formation of microemulsion can't be explained with a single theory. It is considered that the development of complex film over the interface between oil and water by surfactant and co-surfactant ratio is responsible for the spontaneous formation of microemulsion (19). Accordance to Reiss, change in entropy that favors dispersion is greater than the energy required to expand the surface area and the self-emulsification process takes place. The energy needed to develop a new interface between oil and water phase directly affects the free energy of the conventional emulsion (20). Underlying equation gives the corresponding free energy (G) for the emulsification process -

$$\Delta G = \Sigma N \pi r2 \sigma$$

Meanwhile,

'N' denotes the droplets number with radius 'r'.

'σ' describes the interfacial energy. Emulsifying agents stabilize the emulsion through the formation of a monolayer of their droplets that act as a barrier which prevents coalescence and reduces interfacial energy. In order to minimize the interfacial area, both the phases of emulsion gradually separated over time (21). The preceding equation shows that the greater energy level does not favor the spontaneous formation of the oil-water interface. It has not yet been proven that the SEDDS spontaneously emulsifies in a true thermodynamic sense. A technique for quantitative evaluation of ease of emulsification has been designed by measuring the cloudiness of the oil-surfactant system in an aqueous phase by use of phosphate nonyl phenoxy-late (PNE) and phosphate fatty alcohol ethoxylate (PFE) in 1-hexane. This method suggests the emulsification process which might be related to how easily water penetrates the oil-water interface, with the formation of a liquid crystalline phase resulting in swelling at the interface (22). A phase study is needed when there is appearance of liquid crystals in self-emulsification process. It is suggested that efficient formulations typically operated in a region of improved aqueous solubilization and nearby phase inversion (23).

SELECTION OF EXCIPIENTS IN FORMULATION :

Drug

The lipophilicity and hydrophobicity of the drugs are the most significant parameters for SEDDS formulation. The log P of a drug should ideally be ≥ 2. Very large doses of drugs are not suitable for SEDDS unless they show good solubility in at least one if their component (24). Drugs from BCS

class II and IV are predominately adopted for this formulation but all classes may be extended (25), as depicted in Table 1

Table 1: Problems associated in various BCS categories

BCS Class	Problems associated
CLASS I	Enzymatic breakdown, efflux in gut wall
CLASS II	Solubilization and bioavailability
CLASS III	Enzymatic breakdown, efflux in gut wall, and bioavailability
CLASS IV	Solubilization, bioavailability, enzymatic breakdown, and efflux in gut wall

'Rule of five' has been developed by Lipinski and has received more attention as a potential qualitative predictive model for oral absorption patterns. It states that if there are more than five H-bond donors, more than ten H-bond acceptors, molecular weight is greater than 500, and estimated log P is more than 5 then poor absorption or poor permeation more likely to occur in the discovery paradigm (26).

The oil phase

Lipid is a key component in this type of formulation. A greater amount of the lipophilic drug can be absorbed and transported through intestinal lymphatic system, by solubilizing and helping them to self-emulsify (27). After his initial work on SEDDS, Pouton developed the lipid formulation classification system (LFCS) to determine the critical performance parameters of lipid systems depicted in Table 2 (24).

Table. 2: Classification of lipid formulation system

Formulation	Excipients	Properties	Advantages	Dispersion/ particle size
Type I	Oils without the surfactants (e.g di- tri and monoglycerides) 100 % oil	Non dispersing, Requires digestion	GRAS status; simple; excellent capsule compatibility	Corse
Type II	Water and oil-insoluble surfactants (40-80% oil, 20-60% surfactant HLB<12)	SEDDS without water-soluble components	Unlikely encounter solvent capacity on the dispersion	100-250 nm
Type III	Surfactants, co-solvents, and oils (both water-soluble and water-insoluble); (40-80% oil, 20-40% surfactant having HLB>11, 0-40% co-solvent).	SEDDS/SMEDDS with water water-soluble components	Dispersion which is clear or almost transparent; drug absorption without the digestion	100-250 nm
Type IIIA	Surfactants, co-solvents, and oils (both water-soluble and	SMEDDS with minimal oil content and water-	Clear dispersion; drug absorption	50-100 nm

	water-insoluble); (20% oil, 20-50% surfactant having HLB>11, 20-50% co-solvent).	soluble components	without digestion	
Type IV	Water soluble surfactants and co-solvents; (0% oil, 30-100% surfactant, 0-50 % co-solvent).	Formulation disperses typically to form a micellar solution	Excellent drug-solvent compatibility, disperses to form a micellar solution.	< 50 nm

FDA published the GRAS (Generally Recommended as Safe) list in the Code of Federal Regulation (CFR) which provide an extensive database for acceptable excipients with their maximum dose and route of administration for each excipients including lipids. Oils can be turned highly cytotoxic when decreased up to the nano range in situ. Hence scientist must be careful while selecting oils for such systems (28). The physical properties such as melting point and HLB properties of the glycerides are determined through the type of fatty acid and the degree of esterification with regard to glycerol that results in the formation of mono- or di-glyceride. The component of oil is frequently an ester of fatty acid or a medium or long chain saturated/unsaturated hydrocarbons (29). Medium-chain triglycerides (MCTs) have 6-12 carbon chains, which are transported into the systemic circulation via the portal blood, and long-chain triglycerides (LCTs) have more than 12 carbon chain which is transported via the intestinal lymphatic system. As the degree of unsaturation increases, the melting point of oil also get increases resulting increase in relative susceptibility to oxidation. MCTs can prevent oxidation and improve fluidity and solubilizing properties due to reduced degrees of unsaturation. Hence, MCTs are mostly employed for SEDDS formulation (4). Evidently, they have been deemed somewhat less desirable than novel semi-synthetic medium chain derivatives, that are better known as amphiphilic molecules with surface active properties. In such cases, a more lipophilic surfactant may be used in place of hydrophilic oil in the formulation (30). Edible oils which are unmodified give the highly 'natural' relying for lipid-carrier but their inability to dissolve a significant quantity of hydrophobic drugs getting difficulty in attainment of efficient self-emulsification results in their restricted use in SEDDS (31). Hydrolyzed or modified vegetable oils are extensively employed excipients because they produce effective emulsions with a number of surfactants which are recognized for oral administration have improved drug solubility characteristics (32).Commonly used oils in the formulation of SEDDS are shown in Table 3.

Table 3: Commonly used oils in SEDDS formulation

General Class	Examples	Commercial Name
Medium chain	Triglycerides of capric/caprylic acid	Labrafac® CC, Captex® 300, Captex® 350, Crodamol GTCC
Medium chain	Diglycerides of capric/ caprylic acid	Capmul® MCM, Akoline® MCMs
Medium chain	Monoglycerides of capric/caprylic acid	Capryol® 90, Capryol® PGMC, Imwitor® 742
Long chain	Glyceryl monooleate	Capmul® GMO, Peceol®
Long chain	Glyceryl monolenoleate	Maisine® 35

Propylene glycol (PG) fatty acid esters	PG monocaprylate	Capmul® 200, Miglyol® 840
Propylene glycol fatty acid esters	PG monolaurate	Capmul® PG-12, Lauroglycol® 90, Lauroglycil® FCC
Propylene glycol fatty acid esters	PG dicaprylate/caprate	Captex® 200, Miglyol® 840

Surfactants:

Surfactants facilitate dispersion by forming an interfacial film and lowering interfacial tension while formulating the SEDDS. Generally, addition of 30–60% w/w of surface-active agents to the formulation results in improved self-emulsification in GIT. An HLB Value ranging 1-10 indicates more lipophilic and 11-20 indicates more hydrophilic nature.Combinations of Hydrophilic and Lipophilic surface active agents generate optimised HLB Value to formluate oil-in-water or water -in-oil emulsion.The safety aspect of surfactants should be thoroughly considered because, in high concentrations, they may cause irritation to the gastric wall. Natural surfactants are more preferable than synthetic one for safety reasons however, it offers less effective self-emulsification as compared to synthetics (33). Non-ionic surfactants are frequently favored over their ionic counterparts for self-emulsifying formulation preparation owing to more excellent safety profile and improved stability of emulsion across a wider pH range and ionic concentration (34). Though they may produce reversible changes in the mucosal permeability of intestine, still facilitate the co-administered drugs to be absorbed. Commonly used surfactants and in which category they fall are depicted in Table 4. When the amphiphilic nature of surfactants is used in the preparation of SEDDS, can dissolve larger amounts of hydrophobic drugs. By this, the precipitation of drugs in GI lumen can be avoided and the existence of drug molecules can be prolonged (35).

Table 4: Commonly used surfactants in SEDDS formulation

General class	Commercial name
Polysorbates	Tween® 20, Tween® 80
Sorban esters	Span® 20, Span® 80, Crill® 4
Castor oil esters	Cremophor®-EL, Cremophor® RH40, Croduret® 40
Polyglycolyzed glycerides	Labrafil® 1944, Labrasol®

Biosurfactants are promising alternatives to synthetic surfactants due to their minimum toxicity, biodegradability, maximum stability, and good environmental compatibility at different pH and temperature conditions. These are surface-active metabolites of the micro-organism that grow in the water-miscible or oily substrate culture broth or reside on the surface of the micro-organism and are released into the culture broth. The hydrophilic biosurfactant component can be carbohydrates, amino acids, cyclic peptides, alcohol, and phosphate carboxyl acid while a lipophilic portion of the molecule is made up of saturated, unsaturated, linear, branched, or unbranched long-chain fatty acid. Biosurfactants can be classified as Lipopeptides, Glycolipids, Fatty acids, and Polymer types (36,37).

Co-surfactant/Co-solvent :

In majority of cases, it is very difficult for a single surfactant to produce a low interfacial tension, so

it is quiet essential to add co-surfactant or co-solvent. They can work together with surfactants to raise the drug solubility and ability to disperse into oil phase thereby enhancing the stability and uniformity of nano-emulsion (38). Co-surfactant further reduces the transitory negative value of interfacial tension and improves the flexibility of the interfacial film to achieve distinct curvatures for the production of various concentrations of a microemulsion. Preferably, the larger concentration of surfactant may be imitated by the introduction of co-surfactant. When the film seems substantially depleted it absorbs more surfactant or surfactant/co-surfactant ratio allowing spontaneous emulsion to form. The optimal HLB to reduce the o/w interface is 10–14. Most commonly, medium-chain length alcohols (C3-C8) are used as co-surfactant (39). Following aqueous dispersion, co-solvent merely migrates towards the water phase. Additionally, alcohol and other volatile co-solvents may evaporate into capsule shells resulting drug precipitation. Hence, their quantity should be kept to a minimum (40). Table. 5 shows the commonly used co-surfactants in SEDDS formulations.

Table 5: Commonly used co-surfactants in SEDDS formulation

General class	Commercial name
Alcohols	Ethanol, Benzyl alcohol
Polyethylene glycols	PEG 300, PEG 400, PEG 600
Diethylene glycol monoethyl ether	Transcutol® P, Transcutol® HP

The aqueous phase

The composition of the aqueous phase (used in the formulation of SEDDS) has an effect on the droplet size as well as the stability of the water-in-oil emulsion. Depending on the kind of application, it is important to analyze the self-emulsification of the SEDDS as well as the characteristics of the resulting w/o emulsion in aqueous phases with different pH and electrolyte concentrations. (12).

Formulation design of SEDDS

To thoroughly solubilize the drug in liquid self-emulsifying formulations, a micelle or solvent is used which ensures the best possible absorption. They have to instantaneously produce a clear dispersion that remains stable upon dilutions. In these formulations, the drug is dispersed throughout in an inert excipient matrix and may exist in amorphous, solubilized, or finely separated crystals or some combination of these (41).

Silva et. al. hypothesized that the small particle size and the polarity of the resulting oil droplets dictate the effective release of drug molecules from SEDDS (42) and during formulation solubility, dissolution, and permeability correlate the therapeutic effectiveness.

Screening of excipients

Screening of excipients is the most important parameter which can be fulfilled by solubility and it helps in predicting the precipitation of drug in-vivo. It must be checked the solubility in various oils, surfactants, and co-surfactants, and shake flask is most commonly used method. The following goals are achieved by conducting solubility studies (24).

1. Oil, Surfactant and co-surfactant that have the greatest solubilizing capacity for drug can be identified.
2. Optimal drug loading can be achieved by keeping in minimal volume of overall formulation.
3. preventing the degradation or metabolization of the drug in the physiological environment.

By mixing equal quantities of the selected oils and surfactants followed by homogenization reveals the emulsifying ability of Surfactant. Also,

addition of double distilled water to this mixture and minimum number of required flask inversions exhibits the ease of emulsification. The resultant microemulsion should be analyzed further for clarity, turbidity and % transmittance. The co-surfactants should be screened by same method through vortex mixing with selected surfactants and oil phases (43).

Construction of pseudo-ternary phase diagram

The formulation of SEDDS, illustrates change in the system's phase behavior with respect to composition changes, which mainly depends on pseudo-ternary phase diagrams. This illustrates three components that make up a system — oil, surfactant or Smix and water. Each point of the triangle shows 100% of the relevant component. When a fourth component such as co-surfactant, is included, the ternary diagram might be referred to as pseudo-ternary phase diagram. The purpose of the phase diagram is to illustrate the size and characteristics of the microemulsion region (44). The ratio of any two of third or fourth component is retained constant during designing pseudo-ternary diagram and they typically form their three corners. The method of water titration is frequently used to prepare phase diagrams. Optimized Smix is dissolved in oil phase in different ratios varying from 1:9 to 9:1 and then continuously titrated drop by drop with distilled water (45). The mixture's appearance (clarity, opalescence, or isotropy) is noted along with the description of phases and total water consumption needed for it. The amount of water, surfactant and oil is kept in tabular form. Each mixture should have a total 100% concentration across all components. When all points are connected, an area is generated that indicates the monophasic microemulsion existing region and under the broader area, a good emulsification efficacy occurs. A ternary phase diagram having composition A, B and C is shown in Fig 3.

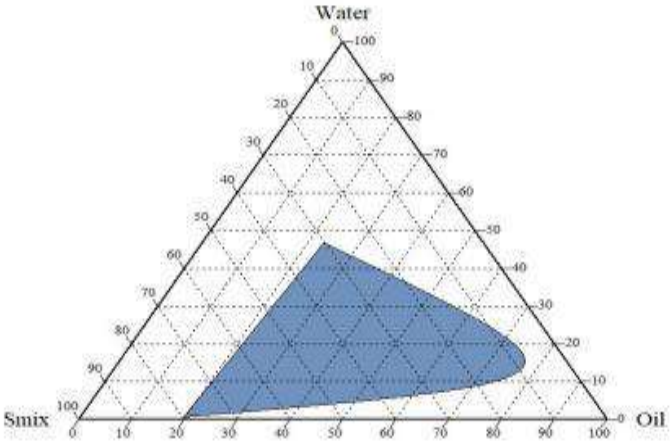

Fig 3: A ternary phase diagram representing all three components at three corners

PREPARATION OF SEDDS

It can be prepared by various methods as follows:

High-pressure homogenizer-

Depending on the high shear stress used, nano-formulations prepared by high pressure results in the development of fine emulsion. Two ideas, namely cavitation, and turbulence, can account for the droplet size. This technique can prepare nano-emulsions with droplet sizes under 100 nm. The content of the sample, the kind of homogenizer with their operating parameters such as energy intensity, time, and temperature, all affect the droplet size of the nano-emulsions. Foods, pharmaceuticals, and biotechnological nano-emulsions are frequently prepared by high-pressure homogenization (46).

High-energy approach-

This technique uses high mechanical energy to prepare nano-emulsions with a combination of ingredients, including oil, surfactants, and co-solvent. The production of nano-emulsions with high kinetic energy produces strong disruptive forces that split apart big droplets into nano-sized (47).

Sonication method –

In terms of cleaning and operation, ultrasonication is superior to other high-energy approaches. Cavitation force produced by ultrasonic waves due to which the droplet size of the emulsion is reduced, and a nano emulsion is formed (48).

Micro-fluidization-

For this approach, a unit of equipment called a micro-fluidizer is needed. The positive displacement propels the product into interaction chamber. Very small droplets of micro- or nano-emulsion will be formed when finished product is delivered through a very small droplet channel called microchannel (49).

CHARACTERIZATION OF SEDDS

1. **Visual assessment:**

This could provide details regarding the mixture's ability to micro-emulsify and the consequences of dispersion, estimation of enhanced drug solubility, and adsorption through wide surface area provided by the emulsion (5). Presence of a clear, isotropic, and transparent solution on addition of distilled water indicates the development of nano-emulsions, whereas the presence of an opaque solution shows the evolution of microemulsions. The formulation is thought to be stable if there is no precipitation and/or phase separation.

2. **Zeta potential measurement:**

The charge contained on movable surface is the zeta potential and it directly relates the stability of emulsion. The formulation is stable at greater zeta potential. Due to presence of fatty acids, oil droplets in typical SEDDS have a negative charge [33]. Zeta potential is frequently determined with Zetasizer, Mastersizer, etc and for this, the formulation is diluted in distilled water at a ratio of 1:2500 (v/v) being constantly stirred (50). In accordance with the Helmholtz-Smoluchowski equation, zeta potential -

$$U = \mathcal{E}\xi Ex/\eta$$

Here,

U = Electrophoretic mobility,

Ɛ = Permittivity,

ξ = Zeta potential,

η = Viscosity,

Ex = Axial electric field

3. **Analysis of droplet size:**

Emulsion droplet size can be measured using a Coulter Nanosizer, a common technique like neutron-scattering, small angle x-ray, or microscopic method. The structural information of micelles between 5-25 nm can be obtained via small angle X-ray scattering (50).

4. **Dispersibility test**

Using standard USP type II dissolution apparatus the efficacy of self-emulsification is assessed. 1 ml of each formulation is added to 500 ml of distilled water at 37±0.50 C. The low intensity agitation is provided by revolving stainless steel paddle at 50 rpm. The grading types mentioned below are used to visually assess the in-vivo of formulation:

- **Grade A:**

A nano-emulsion that forms quickly (within 1 minute) and is transparent or blue in color.

- **Grade B:**

A quickly evolving, slightly less transparent, and blue-looking emulsion.

- **Grade C:**

A thin, creamy emulsion is formed in less than two minutes.

- **Grade D:**

A dull and greyish-white which appears slightly greasy and takes more than two minutes to emulsify.

- **Grade E:**

Formulations with either inadequate, or limited emulsification and visible surface oil beads.

When it distributed in GIT, Grade A and Grade B will remain as nano emulsion whereas Grade C may be indicated for SEDDS formulation (51).

5. Turbidometric evaluation

This determines how quickly the dispersion gets equilibrium and distinguishes the self-emulsification efficiency. To check the clarity of generated nano/micro-emulsion and emulsification time, the optical clarity of the formulation is measured every 15 seconds using Orbeco-Helle and the Hach turbidity meters, which is connected to a dissolving apparatus. The absorbance of a sufficiently diluted aqueous dispersion at specific wavelength can also be used to determine turbidity (51).

6. Viscosity determination

Using a cone and plate viscometer with a spindle or, the Brookfield viscometer measures the rheological characteristics of emulsion. The lower viscosity shows that formulation is o/w type and when it is higher, an emulsion is a w/o type. (51).

7. Determination of emulsification time

USP type II dissolution apparatus may be used for emulsification time determination. The formulation is poured into a water-filled vessel, which is kept at 370C though being gently stirred (100 rpm). Time needed to form a clear dispersion is documented as the emulsification time (51). The concentration of oil and surfactant determines how long it takes to emulsify.

8. Thermodynamic stability and measurement

The primary concern with a lipid-based formulation is its physical stability, which might be negatively affected by drug precipitation inside its excipient matrices. Compatibility issues between the formulation cause deformation, latency in the disintegration of the drug, or an inadequate release of the drug (51,52).

a. **Heating-cooling cycle –**

Six cycles of cooling and heating are carried out between refrigerated condition (40C) and high temperature (450C), with exposure at each temperature lasting at least 48 hours.

b. **Centrifugation –**

Formulations that have completed the heating-cooling cycle, gone through centrifuge for half hour at 3000-3500 rpm. The freeze-thaw stress test is performed on formulations those do not exhibit any phase separation.

c. **Freeze-thaw cycle –**

Three cycles between -210C to 250C, with storage at every temperature for at least 48 hours. Formulations that pass these tests demonstrated have an adequate stability and no phase separation, cracking, or creaming.

9. Determination of cloud point

The homogeneous solution at which it loses their transparency, known as cloud point. Surfactants usually lose their ability to prepare micelles above the cloud point. The formulations are diluted with distilled water in ratio of 1:100 (v/v) and then kept into oil or water bath. The temperature is elevated gradually at the rate of 50C/min starting from 250C. The cloud point then observed visually when sudden turbidity or cloudiness appeared (53).

10. Refractive index (RI) and percentage transmittance

On a glass slide, a drop of formulation is placed, and its RI is calculated by contrasting it with water (1.33). The percent transmittance can be quantified at a particular wavelength using UV-spectrophotometric detection with distilled water as blank. When it is greater than 99%, formulation may be considered as transparent (53).

11. Robustness to dilution

The formulation is referred robust to dilution if, after dilution with several dilution factors and dissolution media, there is no phase separation or,

drug precipitation even after more than 12 hours of storage. (53).

12. In-vitro diffusion

This study is conducted to evaluate the release pattern of formulations using dialysis technique selecting phosphate buffer as a medium. One end of dialysis membrane is threaded, and 1 ml formulation along with 0.5 ml of dialysing medium is placed inside membrane. The other end of the membrane is also tied with thread to form a candy-like structure, and allowed to rotate at 100 rpm in dialyzing media using a magnetic stirrer or other suitable dissolution apparatus. At various time intervals, samples are pipetted out and replaced with the same volume of the fresh dialyzing media. Samples are analyzed for drug release after appropriate dilution (54).

13. In vitro dissolution

A USP type II dissolution apparatus is used for the quantitative in-vitro dissolution study. There is a vessel having 500 cc of simulating gastric fluid as media and it is set to rotate at 50 rpm and 37±0.50C. At regular intervals, samples are withdrawn, and replaced with the fresh medium. The sample then analysed by using a suitable analytical technique. The in vitro dissolution study is mainly used to predict the rate and extent of absorption of poorly water- soluble drug.

14. In-vitro permeation study

The parallel artificial membrane permeability model (PAMPA) and CACO-2 cell model are widely used to assess in-vitro drug permeation. PAMA is considered as high-throughput technique that predicts passive oral drug absorption using an artificial lipidic membrane (55).

SOLID SELF-EMULSIFYING DRUG DELIVERY SYSTEM (S-SEDDS)

Solidification can stabilize macromolecules like proteins and peptides for oral administration. Tang et al. (16) discussed the role of S-SEDDSs in inhibiting first-pass metabolism, p-gp efflux, lymph targeting, controlled drug release, prolong gastric residence time, and increase permeability in detail. There are different solidification techniques (56) exist that allow liquid or semi-solid formulations to be converted into solid particles that can be filled into capsules, sachets, or tablets.

i. **Spray drying –**

This technique involves mixing lipids, surfactant, and drugs with carriers and then solubilizing the mixture before spray dried. The solubilized liquid formulation is then atomized into a spray of droplets. The droplets have to go through the drying chamber, where the volatile vehicle undergo evaporation, resulting in the formation of tiny solid particles which can be converted into tablets by compression or filled in capsules. Spray drying was used to produce a Nimodipine self-micro emulsifying formulation with dextran as a solid carrier. Spray drying aids in reducing average particle size to an optimum for maximum solubilization in aqueous media. This technique can produce solid SEDDS from a variety of solid carriers, whether hydrophobic or hydrophilic (57,58).

ii. **Spray cooling/ Spray congealing –**

It entails preparing a molten formulation by combining lipids, surfactants, and drugs, which are then sprayed into a cooling chamber. When these molten droplets interact with cooling air, they congeal and re-crystallize into spherical solid particles that obtained as fine powders at the bottom and can be utilized to produce solid dosage forms. Different atomizers can be used to atomize the mixture of liquid generating droplets, but ultrasonic atomizers are most common (59).

iii. **Adsorption on solid carriers –**

Liquid SEDDS can be adsorbed (up to 70% w/w) on solid carriers, which may be microporous inorganic substances, colloidal inorganic adsorbents, cross-linked (CL) polymers with a high surface area or nanoparticle adsorbents such as silica, silicates and hydroxide of magnesium,

talcum, cross-povidone, CL sodium CMC and polymethyl methacrylate (29).

iv. **Melt granulation –**

The technique is used to prepare powder agglomeration with incorporation of a binder. At relatively low temperature (50-800C), the binder got softened. As a one-step process, it has numerous benefits over traditional wet granulation, which exclude the addition of liquid parts and subsequent drying process. Process parameters such as the time of mixing, binder viscosity, and particle size are the few variables to be controlled (60).

v. **Freeze drying/lyophilization –**

An innovative method of solidifying liquid or semi-solid SEDDS materials is freeze drying, also known as cryodesiccation. A frozen aqueous phase existing in liquid SEDDS can be sublimated using this procedure at relatively lower temperature and pressure to form powder which, when reconstituted with an aqueous phase, produces a fine micro- or nano-emulsion. In order to create a lyophilized molecular dispersion, the product is frozen to solidify before the solvent is evaporated through sublimation. The benefits of the lyophilized SEDDS include better stability of drug, efficacy, handling and patient satisfaction (61).

vi. **Spheronization on Extrusion/Melt Extrusion –**

Extrusion is a solvent-free process which turns plastic raw materials into an agglomeration that exhibits cylindrically formed grains. The formulation is mixed with a carrier or adsorbent excipient, and then extrudes are broken down and transformed into spherical particles through sequential agglomeration and spheronization. These spheroids or pellets often show minimal friability, excellent flowability, a smaller particle size range, and high drug loading (62,63).

vii. Electrospray technique –

This is referred to as a promising drug delivery mechanism for encapsulating the bioactive compound that is poorly water-soluble. The electro-spraying device includes a stainless receptor, a plastic syringe for holding the lipid formulation, a constant flow pump, and a variable high-voltage power source. Work on Diosmetin-loaded solid SEDDS was done by utilizing PVP as the carrier (64).

viii. Filling of capsules with liquid or semi-solid SEDDS –

Filling of liquid or semi-solid SEDDS in capsule shell for oral administration is the most simple and popular approach for encapsulation. Alza Corporation has developed Liquid-Oros technology for the controlled release. This liquid self-emulsifying system is based on the osmotic principle. It is composed of an osmotic layer that pushes the drug formulation through an opening in the hard or soft capsule when it comes into contact with water (65).

SEDDS in various dosage forms

1. **Self-emulsifying capsules –**

Capsules containing liquid SEDDS spontaneously produce droplets of microemulsion on administration that disperse in the GIT. Liquid SEDDS have been transformed into S-SEDDS by a number of formulation scientists and placed in capsules (65).

2. **Self-emulsifying tablets –**

Adsorption of nano/microemulsion on granulating materials is required for the development of self-emulsifying tablets, which are subsequently compressed. The optimized self-emulsifying tablet's dissolution profile indicated that 80-90% drug released in 45 minutes. The SE osmotic pump tablet is the most recent development of self-emulsifying tablets, where the elementary osmotic pump system is selected as the carrier of self-emulsifying (SE) system.

3. Self-emulsifying beads –

In SE system, solid dosage forms can be obtained by forming beads with minimum quantity of excipients. Beads are created through the copolymerization of the monomers divinyl benzene and styrene. It is stable across a wide pH, temperature, and humidity range, chemically inert, and biocompatible. The loading efficacy and in-vitro drug release are controlled by the geometrical characteristics of porous materials and bead size (66).

4. **Self-emulsifying hybrid microparticles**

These systems are colloidal solid, self-emulsifying mixtures of medium-chain triglycerides with diameters varying from 3 to 100 nm. Microparticles are created by spray-drying lipidic emulsions containing colloidal silica particles and positively charged lipophilic surfactants in an aqueous phase. As a result of the cationic charge on the surface, it has the advantages of increased drug loading, higher drug absorption, and improved drug stability (66,67).

5. **Self-emulsifying nanoparticles –**

SE nanoparticles contain oily liquid mixtures. Such formulations are produced using a solvent injection technique and a suitable mixture of polymers, like polyglycolic acid (PGA), polylactic acid (PLA), and polylactic-co-glycolic acid (PLGA). The nanoparticles provide a controlled drug delivery profile, improved gastric fluid stability, and higher oral bioavailability. These formulations inadvertently produce o/w microemulsions when they come in contact with gastro-intestinal fluids (66).

6. **Self-emulsifying liposphere –**

Several solid self-emulsifying lipospheres containing piroxicam were developed using various homolipid and Tween 65 ratios. Dissolution profile, particle size and absolute drug content, are used to characterize the self-emulsifying lipospheres (7).

7. **Self-emulsifying implants –**

Co-polymer based SE implants exhibit self-emulsifying properties without the use of an emulsifier. These copolymers provide excellent sealant for implantable prostheses (7).

8. **Semisolid SEDDS –**

Semisolid SEDDS do not require co-surfactants and are produced using lipidic components similar to those used in liquid formulation, but greater melting point at room temperature. The most common surfactants and lipids used in the development of semisolid SEDDS are laurul macrogol-glycerides including gelucire 44/14 and gelucire 50/13, derivatives of polyoxyethylene hydrogenated castor oil. These preparations are more viscous than the corresponding liquid one, which increases the stability and mobility of the medication while being handled (66,67).

9. **Dry emulsion –**

It is typically an oil-water emulsion that can be spray dried or use of solid-carrier adsorption or could be dispersed in water before use. These are basically in powder form and emulsification takes place either naturally in biological systems or as a result of contact with an aqueous solution. Stability concern of conventional can effectively be resolved by dry emulsion and also minimize the use of potentially harmful organic solvents (66,67). Lipid-based formulations have quickly become popular due to performance and continual advancements in manufacturing methods. There are several medications already existed for commercial use is shown in Table 6.

Table 6: Commercially available marketed formulation of SEDDS

Brand name	API	Company	Dosage Form
Neoral	Cyclosporin A	Novartis	SGC
Norvir	Ritonavir	AbbVie	SGC
Depakene	Valproic acid	AbbVie	SGC
AGengraf	Cyclosporin A	Abbott	HGC

Sandimmune	Cyclosporin A	Novartis	SGC
Kaletra	Lopinavir & Ritonavir	Abbott	HGC
Fortovase	Sanquinavir	Roche	SGC
Vesanoid	Tretinoin	Roche	SGC
Isotretinoin Accutane	Isotretinoin	Roche	SGC
Panimum bioral	Cyclosporine	Panacea Biotec	SGC/HGC

FUTURE ASPECTS :

SEDDS AS NANOCARRIER TO ENHANCE MUCUS PERMEABILITY:

Extensive research has focused recently on the use of SEDDS as a nano-carrier to enhance the mucus permeability.One of the example is the oral transport of peptide are the mucus barrier and mucosal enzymes (68).Any therapeutic agent delivered through the mucosal membrane must pass through mucosa to reach the underneath epithelium and then be subsequently absorbed to the systemic circulation (69). Proteins and peptides are more susceptible to mucus entrapment or degradation by protease enzyme within the mucus layer (70). Such therapeutic compounds can better diffuse through the mucus barrier and offer protection against enzymatic degradation when incorporated into suitable nano-system (71). Fig 4. indicates the barrier of intestinal layer for delivery of macromolecules like peptides. Hence, an ideal nano-carrier like SEDDS will prevent mucus entrapment for mucosal delivery (72) and protect the loaded drugs from enzymatic degradation facilitating their permeation through intestinal mucus barrier (73,74). Mucolytic agents may significantly increase the passage of SEDDS across the barrier by reversible disruption of mucin network (75,76). Here incorporating and releasing of these agents from SEDDS reduce the mucosal resistance towards the permeation of NPs or SEDDSs (77). Improved permeability of SEDDS through mucus has been achieved by using three different types of mucolytic agents (78). First, substances that dissolve the disulfide bonds in the network of mucins, eg - N-acetyl cysteine (NAC), dithiothreitol, and glutathione. Second, the proteolytic agent breaks the peptide bond present between mucins such as bromelain, trypsin, and papain. Third, the substances called DNA hydrolyzing agents separate DNA strands entangled in the mucin network (79). These are being investigated as a delivery system for hydrophilic macromolecules that are administered orally but are susceptible to intestinal rapid hydrolysis. These hydrophilic substances are converted into hydrophobic by process of Hydrophobic Ion Pairing (HIP) before being placed in oil phase. (80). Peptides are combined with a macromolecular hydrophobic counter ion in this HIP technique to produce hydrophobic agents with significant oil solubility. Loading of peptides into SEDDS has been improved through subsequential studies into HIP of peptides. For instance, Griesser et al. reviewed the efficacy of various ion-pairing surfactants in complexing with various peptides like insulin, desmopressin and leuprorelin (81). Due to the good encapsulation and sustained release capability, SEDDS can offer efficient resistance against enzymatic degradation. This makes unavailable free peptides which further reduce their enzymatic hydrolysis in intestine (82). The charge present on the surface of oil droplet has a major impact on SEDDS diffusivity as similar to solid NPs (83). A negatively charged droplet at the intestinal epithelial interface would significantly reduce the endocytosis mediated absorption (84). There are methods for measuring SEDDS diffusion through mucus barrier. For researchers, quantifying SEDDS diffusion over the mucus barrier was quite challenging (85). It is possible that atmospheric

conditions make mucus samples dryer or more humid when they are being tested in vitro, which could affect the diffusion of droplets across mucosa (86). The techniques using a Transwell chamber, Multiple Particle Tracking, Rotating Silicon Tube, Fluorescence Recovery After Photo-bleaching, etc. are widely employed to evaluate the mucus permeation of SEDDS across a static layer (87).

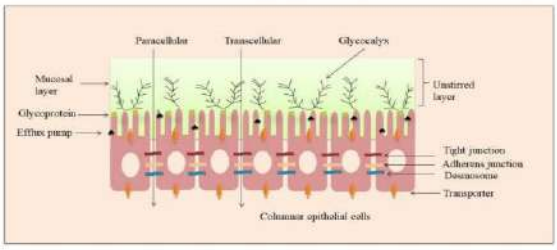

Fig 4: Mucus permeation through intestinal barrier

CONCLUSION

We conclude from the overview provided that Lipid based drug delivery systems particularly self-emulsifying drug delivery system (SEDDS) is an acceptable method to formulate poorly aqueous soluble drugs and to facilitate their lymphatic transport for better absorption. Smaller droplet sizes play an important role in enhancing the bioavailability of drugs in systemic fluid and allow for faster and more improved drug release.

Medium-chain triglycerides can improve fluidity and prevent oxidation hence they are frequently employed for these formulations. While selecting suitable excipients for their formulation, the safety aspects must be thoroughly considered in terms of their types and concentration. Natural edible oils are the most reliable candidates however their inability to dissolve significant amounts of hydrophobic drugs. Surfactants that are non-ionic are typically preferred over ionic. In recent years, biosurfactants became a promising substitute due to their lesser toxicity and biodegradability. Despite the advancements, the lack of a suitable in-vitro model which helps in explaining whether the drug dissolved in GIT or not, is a major obstacle to evaluate SEDDS. The formulated SEDDS can be characterized for their clarity, dispersibility, self-emulsification time, thermodynamic stability, and in-vitro/in-vivo assessment.

Recently, an ample of research has focused on using SEDDS as nano-carrier to increase mucus permeability. This system can be extensively utilized to enhance the permeation of drugs particularly those which are prone to enzymatic degradation like proteins and peptides. Therefore, these approaches may improve the rate and extent to which lipophilic drugs get absorbed leading to a more uniform blood-time profile having dissolution rate limited absorption.

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