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RECENT FRONTIERS IN SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT: Oral route has always been the preferred route of drug administration in many diseases. This route is limited to those drugs molecules that are permeable across the gastric mucosa and are sparingly soluble. Solubility is an important parameter to achieve the desired concentration of drug in systemic circulation for therapeutic response. As a consequence of modern drug discovery techniques, there has been a steady increase in the number of new active lipophilic compounds that are poorly water-soluble. It is a challenge for a scientist to convert those molecules into an orally administered formulation with sufficient bioavailability. Improving oral bioavailability of poorly water-soluble drugs using self micro emulsifying drug delivery systems (SMEDDS) appears most promising. Currently, various technologies are available to deal with insoluble drugs such as micronization, solid dispersions, complex formation, *etc*. Among the several approaches, SMEDDS has emerged as a distinctive approach used to improve the bioavailability of hydrophobic drugs. SMEDDS is isotropic mixture of drug, surfactants, cosurfactants, and oil which have unique ability to form fine o/w microemulsion on slight shaking followed by dilution with gastrointestinal fluid. *In-vitro* features such as concentration of surfactants, ratio of oil to surfactant, zeta potential, and size of droplet play a crucial role in drug absorption orally. The present article compiled comprehensively which gives a complete overview of SMEDDS as a promising approach to effectively tackle the problem of poorly soluble molecules. It also provides a discussion on recent developments in SMEDDS and solid SMEDDS, their characterization and applications.

INTRODUCTION: As a consequence of modern drug discovery techniques, there has been a steady increase in the number of new pharmacologically active lipophilic compounds that are poorly water-soluble. About 40% of new drugs exhibit poor water solubility, resulting in lack of dose proportionality, high inter- and intra-subject variability, and low oral bioavailability.

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For the pharmaceutical preparation to succeed in the market, it should fulfill all the criteria such as stability, patient compliance, cost of the product, and bioavailability. It is a great challenge for pharmaceutical scientists to convert those molecules into orally administered formulations with sufficient bioavailability.

There are several approaches for improvement in bioavailability, such as the use of crystal polymorphism, surfactants, salt formation, pulverization, size reduction of particles, solid dispersion, microemulsion, liposomes, complex formation, nano-particles, nano and micro-spheres, use of prodrugs and use of permeation enhancer [1]. The main problem with micronization is

chemical/thermal stability; many drugs may degrade and lose activity when they are micronized by a conventional method. For solid dispersion, the amount of carriers used is often large, and thus if the dose of the active ingredient is high, the tablets or capsules formed will be large in volume and difficult to swallow.

Moreover, since the carriers used are usually expensive and freeze-drying or spray-drying method requires particular facilities and processes, leading to high production cost. Though the traditional solvent method can be adopted instead, it is difficult to deal with co-precipitates with high viscosity. Complexation with cyclodextrins techniques is not applicable for drug substances that are not soluble in both aqueous and organic solvents. Realization that the oral bioavailability of poor water-soluble drugs may be enhanced when co-administered with a meal rich in fat has led to increasing recent interest in the formulation of poorly water-soluble drugs in lipids. Lipid suspension, solutions and emulsions have all been used to enhance the oral bioavailability but, more recently, preparation of formulations with lipid base to improve the oral bioavailability of drugs with poor aqueous solubility is in trend. One of the most popular and commercially viable formulations approaches for solving these problems is self-micro emulsifying drug delivery systems (SMEDDS).

SMEDDS have been shown to be reasonably successful in improving the oral bioavailability of poorly water-soluble and lipophilic drugs. Lipid-based drug delivery systems have gained considerable interest after the commercial success of Sandimmun NeoralTM (Cyclosporine A) Fortovase (Saquinavir) and Norvir (Ritonavir) [2].

SMEDDS is the isotropic mixture of cosolvents/cosurfactants, solid or liquid surfactants, one or more hydrophilic solvents, and natural or synthetic oils. These result in the formation of o/w type emulsion or microemulsion in gastrointestinal tract (GIT) due to agitation, which is provided by gastric and intestine motility during digestion, which is necessary for self-emulsification [3].

After per oral administration, these systems form fine microemulsions in GIT with mild agitation provided by gastric mobility, and it has a droplet size between 10–200 nm, transparent than those of conventional emulsions (1-20 μm) which is opaque as shown in **Fig. 1**. These are stable preparations and improve the dissolution of the drug due to increased surface area on the dispersion and solubility effect of surfactants. However, these formulations are normally prepared as liquids that produce some disadvantages such as high production costs, low stability and portability, low drug loading, irreversible drugs/excipients precipitation, and few choices of dosage forms. More importantly, the large quantity (30–60%) of surfactants in the formulations can induce gastrointestinal (GI) irritation.

To address these problems, S-SMEDDS have been investigated as an alternative approach. These systems require the solidification of liquid self-micron emulsifying (SME) ingredients into powders/nanoparticles, which can be converted to various solid dosage forms SME tablets, SME pellets, and so on. Thus, S-SMEDDS will have combined advantages of SMEDDS such as enhanced solubility and bioavailability and with those of solid dosage forms, such as low production cost, convenience of process control, high stability reproducibility and better patient compliance [4].

History of Micron Emulsions: The term microemulsion was first used by TP Hoar and JH Shulman, professors of chemistry at Cambridge University, in 1943. Alternative names for these systems are often used, such as transparent emulsion, swollen micelle, micellar solution, and solubilized oil. Microemulsions are formed when (i) The interfacial tension at the oil/water interface is brought to a very low level, and (ii) The interfacial layer is kept highly flexible and fluid. These two conditions are usually met by a careful and precise choice of the components and of their respective proportions and by the use of a "co-surfactant" which brings flexibility to the oil/water interface.

These conditions lead to a thermodynamically optimized structure, which is stable as opposed to conventional emulsions and does not require a high input of energy to be formed. Because the size of the particles is much smaller than the wavelength of visible light, microemulsions are transparent, and their structure cannot be observed through an optical microscope [5].

FIG. 1: SELF- MICRO EMULSIFYING DRUG DELIVERY SYSTEMS

Need of SMEDDS: Oral delivery of poorly water-soluble compounds is to pre dissolve the compound in a suitable solvent and fill the formulation into capsules. The main benefit of this approach is that pre dissolving the compound overcomes the initial rate-limiting step of particulate dissolution in the aqueous environment within the GI tract. However, the potential problem is that the drug may precipitate out of solution when the formulation disperses in the GI tract, particularly if a hydrophilic solvent is used (*e.g.*, polyethylene glycol). If the drug can be dissolved in a lipid vehicle, there is less potential for precipitation on dilution in the GI tract, as partitioning kinetics will favor the drug remaining in the lipid droplets. Another strategy for poorly soluble drugs is to formulate a solid solution using a water-soluble polymer to aid solubility of the drug compound. For example, polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG 6000) has been used for preparing solid solutions with poorly soluble drugs. One potential problem with this type of formulation is that the drug may favor a more thermodynamically stable state, which can result in the compound crystallizing in the polymer matrix. Therefore the physical stability of such formulations needs to be assessed using techniques such as Differential scanning calorimetry or X-ray crystallography. SMEDDS is a novel approach and is being extensively used to enhance the solubility and bioavailability of poorly water-soluble drugs. In addition to this, the formulated SMEDDS will also prevent the drug from the hostile gastric environment, which will further help in better systemic absorption [6].

Lipid Formulation Classification System: The different lipid drug delivery systems available include lipid solution, lipid emulsion, microemulsion, and dry emulsion. To get a clear picture of all these different systems and due to a large number of possible excipient combinations that may be used to assemble these lipid-based formulations, self-emulsifying systems, in particular, a classification system have been established called as lipid formulation classification system (LFCS). This classification helps to better understand the fate of different lipid formulation in vivo; it also helps to use a systematic & rational formulation approach avoid "trial-and-error "iterations and provide a framework to guide regulatory agencies.

LFCS was established by Pouton in 2000 and recently updated in 2006. [7] The LFCS classifies lipid-based formulations into four types according to their composition and the possible effect of dilution and digestion on their ability to prevent drug precipitation, as shown in **Table 1**.

TABLE 1: LIPID FORMULATION CLASSIFICATION SYSTEM AS DESCRIBED BY POUTON

Composition	Type - I	Type - II	Type - IIIA	Type - IIIB	Type - IV
Glycerides (TG, DG, MG)	100%	40-80%	40-80%	<20%	-
Surfactants (HLB < 12)	-	20-60%	-	-	0-20%
(HLB > 12)	-	-	20-40%	20-50%	20-80%
Hydrophilic co-solvents	-	-	0-40%	20-50%	0-80%
Particle size of dispersion (nm)	Coarse	100-250	100-250	50-100	< 50
Significance of aqueous dilution	Ltd. importance	Solvent capacity unaffected	Some loss of Solvent capacity	Significant phase changes and potential loss of solvent capacity	Significant phase changes and potential loss of solvent capacity
Significance of digestibility	Crucial need	Not crucial but likely to occur	Not crucial but may be inhibited	Not required	Not required

Type I systems consist of formulations which comprise drug in solution in triglycerides and/or mixed glycerides or in an oil-in-water emulsion stabilized by low concentrations of emulsifiers such

as 1% (w/v) polysorbate 60 and 1.2% (w/v) lecithin. Generally, these systems exhibit poor initial aqueous dispersion and require digestion by pancreatic lipase in the GIT to generate more amphiphilic lipid digestion products and promote drug transfer into the colloidal aqueous phase. Type I lipid formulations, therefore, represent a relatively simple formulation option for potent drugs or highly lipophilic compounds where drug solubility in oil is sufficient to allow incorporation of the required dose.

Type II lipid formulations constitute SEDDS. Self-emulsification is generally obtained at surfactant contents above 25% (w/w). However, at higher surfactant contents (greater than 50–60% (w/w) depending on the materials, the progress of emulsification may be compromised by the formation of viscous liquid crystalline gels at the oil/water interface. Type II lipid-based formulations provide the advantage of overcoming the slow dissolution step typically observed with solid dosage forms and as described above generate large interfacial areas which in turn allows efficient partitioning of a drug between the oil droplets and the aqueous phase from where absorption occurs.

Type III lipid-based formulations, commonly referred to as self-microemulsifying drug delivery systems (SMEDDS), are defined by the inclusion of hydrophilic surfactants (HLB>12) and co-solvents such as ethanol, propylene glycol, and polyethylene glycol. Type III formulations can be further segregated into Type IIIA and Type IIIB formulations in order to identify more hydrophilic systems (Type IIIB) where the content of hydrophilic surfactants and co-solvents increases and the lipid content reduces. Type IIIB formulations typically achieve greater dispersion rates when compared with Type IIIA although the risk of drug precipitation on the dispersion of the formulation is higher given the lower lipid content.

Type IV: In order to capture the recent trend towards formulations which contain predominantly hydrophilic surfactants and cosolvents, this category was recently added Type IV formulations do not contain natural lipids and represent the most hydrophilic formulations. These formulations commonly offer increased drug payloads when compared to formulations containing simple glyceride lipids and also produce very fine dispersions when introduced in aqueous media. Little is known, however, as to the solubilization capacity of these systems *in-vivo* and in particular whether they are equally capable of maintaining poorly water-soluble drug in solution during passage along with the GIT when compared with formulations comprising natural oils (Type II and Type III). An example of a Type IV formulation is the current capsule formulation of the HIV protease inhibitor amprenavir (Agenerase), which contains TPGS as a surfactant and PEG 400 and propylene glycol as co-solvents.

Difference between Self Emulsifying Drug Delivery Systems and Self Micro Emulsifying Drug Delivery Systems: SMEDDS are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants that have a unique ability to form fine oil-in-water (o/w) microemulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids. SMEDDS spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification [8]. Other differences between SEDDS and SMEDDS is given in **Table 2**.

TABLE 2: DIFFERENCE BETWEEN SEEDS AND SMEDDS

S. no.	SEDDS	SMEDDS
1	Can be a simple binary formulation with the drug and lipidic excipients able to self emulsify in contact with Gastrointestinal fluids Or A system comprising Drug, surfactant, oil	Are composed of the Drug compound, Surfactant, Co-surfactant, and Oil
2	Lipid droplets size in the dispersion ranges from 200nm- 5µm providing a large surface area for absorption	Lipid droplets size in the dispersion is< 200nm Providing a large surface area for absorption
3	The dispersion has a turbid appearance	The dispersion has an optically clear to translucent appearance
4	SEEDS systems are not Thermodynamically stable in water or physiologic conditions	SMEEDS systems are Thermodynamically stable in water or physiologic conditions

Advantages of SMEDDS: [9]

Improvement in Oral Bioavailability: Dissolution rate dependant absorption is a major factor that limits the bioavailability of various poorly water-soluble drugs. The ability of SMEDDS to present the drug to GIT in the solubilised and micro emulsified form (globule size between 1-100 nm) and subsequent increase in the specific surface area enable more efficient drug transport through the intestinal aqueous boundary layer and through the absorptive brush border membrane leading to improved bioavailability. In SMEDDS, the lipid matrix interacts readily with water, forming a fine particulate oil-in-water (o/w) emulsion. The emulsion droplets will deliver the drug to the gastrointestinal mucosa in the dissolved state readily accessible for absorption. Therefore increase in AUC, *i.e.,* bioavailability and C max, is observed with many drugs when presented in SMEDDS. SMEDDS present drugs in small droplet size and well-proportioned distribution and increase the dissolution and permeability. E.g. In the case of halofantrine, approximately 6-8 fold increase in bioavailability of drugs was reported in comparison to the tablet formulation.

Ease of Manufacture and Scale-Up: SMEDDS require very simple and economical manufacturing facilities like a simple mixer with agitator and volumetric liquid filling equipment for large-scale manufacturing. This explains the interest of industry in the SMEDDS.

Reduction in Inter-Subject and Intra-Subject Variability and Food Effects: There are several drugs that show large inter-subject and intra-subject variation in absorption, leading to decreased performance of drug and patient non-compliance. Food is a major factor affecting the therapeutic performance of the drug in the body. SMEDDS are a boon for such drugs.

Ability to Deliver Peptides that are Prone to Enzymatic Hydrolysis in GIT: One unique property that makes SMEDDS superior as compared to the other drug delivery system is their ability to deliver macromolecules like peptides, hormones, enzyme substrates, and inhibitors and their ability to offer protection from enzymatic hydrolysis. The intestinal hydrolysis of prodrug by cholinesterase can be protected if polysorbate 20 is an emulsifier in microemulsion formulation. These systems are formed spontaneously without aid of energy or heating [19,] thus suitable for thermolabile drugs such as peptides.

No Influence of Lipid Digestion Process: Unlike the other lipid-based drug delivery systems, the performance of SMEDDS is not influenced by the lipolysis, emulsification by the bile salts, action of pancreatic lipases and mixed micelle formation. SMEDDS are not necessarily digested before the drug is absorbed as they present the drug in micro-emulsified form, which can easily penetrate the mucin and water unstirred layer**.**

Increased Drug Loading Capacity: SMEDDS also provide the advantage of increased drug loading capacity when compared with conventional lipid solution as the solubility of poorly water-soluble drugs with an intermediate partition coefficient (2<log P>4) are typically low in natural lipids and much greater in amphiphilic surfactants, co-surfactants and co-solvents.

Avoids First Pass Metabolism: Fine oil droplets empty rapidly from the stomach and promote the wide distribution of drugs throughout the intestinal tract and thereby minimizing irritation frequently encountered with extended contact of drugs and gut wall. When the polymer is incorporated in the composition of SMEDDS, it gives a prolonged release of medicament. Furthermore, because drugs can be loaded in the inner phase and delivered to the lymphatic system, it can bypass the first-pass metabolism. Thus SMEDDS reduces the presystemic clearance in the GI mucosa and hepatic first-pass metabolism. Selective targeting of the drug(s) toward specific absorption window in GIT can also achieve.

Advantages of SMEDDS over Emulsion: [10]

- ✓ SMEDDS not only offer the same advantages of emulsions of facilitating the solubility of hydrophobic drugs but also overcomes the drawback of the layering of emulsions after sitting for a long time. SMEDDS can be easily stored since it belongs to a stable thermodynamics system.
- ✓ Microemulsions formed by the SMEDDS exhibit good thermodynamics stability and

optical transparency. The major difference between the microemulsions and common emulsions lies in the particle size of droplets. The size of the droplets of common emulsion ranges between 0.2 and 10 μm, and that of the droplets of microemulsion formed by the SMEDDS generally ranges between 2 and 100 nm (such droplets are called droplets of nanoparticles). Since the particle size is small, the total surface area for absorption and dispersion is significantly larger than that of solid dosage form, and it can easily penetrate the gastrointestinal tract and be absorbed. The bioavailability of the drug is, therefore, improved.

- ✓ SMEDDS offer numerous delivery options like filled hard gelatin capsules or soft gelatin capsules or can be formulated into tablets, whereas emulsions can only be given as an oral solutions.
- ✓ The emulsion cannot be autoclaved as they have phase inversion temperature while SMEDDS can be autoclaved.

Disadvantages of SMEDDS: [11]

- ✓ Lack of good predictive *in-vitro* models for assessment of the formulations. This *in-vitro* model needs further development and validation before its strength can be evaluated.
- ✓ Further development will be based on *in-vitro* – *in-vivo* correlations, and therefore different prototype lipid-based formulations need to be developed and tested *in-vivo* in a suitable animal model.
- ✓ Another is chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%), which irritate GIT.
- ✓ Moreover, volatile co-solvents in the conventional self-microemulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.
- ✓ The precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent.

Mechanism of Self-Emulsification: According to the researches of Reiss, Self emulsification occurs, when the entropy change occurs**,** dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of conventional emulsion formation is a direct function of the energy required to create a new surface between the two phases and can be described by equation [2].

$$\Delta G = \Sigma N i \pi r^2 \sigma$$

Where, ΔG – free energy accompanying the process (apart from the free energy of mixing),
N – Total number of droplets,
r – Radius of the droplets,
σ – Energy at the interface.

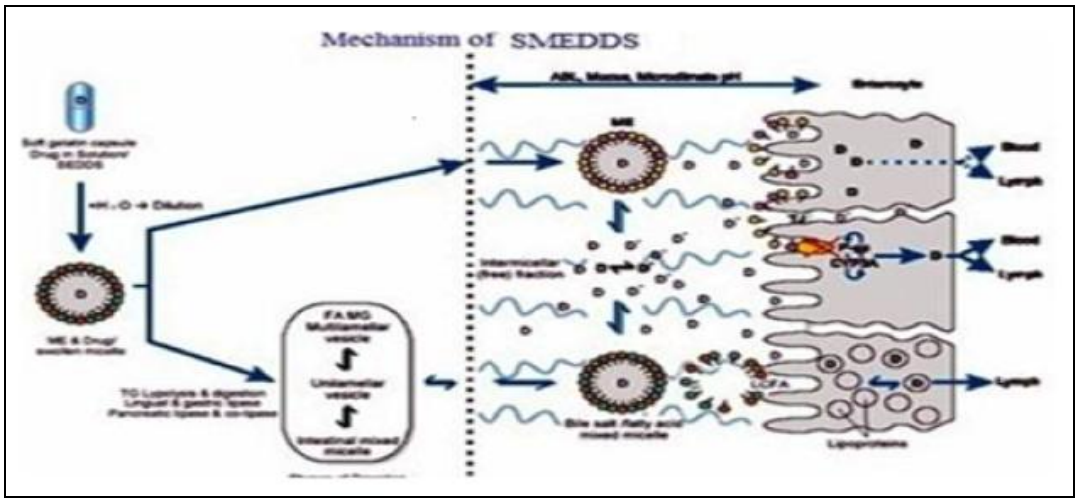

FIG. 2: MECHANISM OF SELF MICROEMULSIFYING DRUG DELIVERY SYSTEM

The two phases of the emulsion will tend to separate in order to reduce the interfacial area and, subsequently, the free energy of the system. Therefore, the emulsions resulting from aqueous dilution are stabilized by conventional emulsifying agents, which form a monolayer around the emulsion droplets and hence, reduce the interfacial energy, as well as providing a barrier to coalescence. For emulsification to occur, it is necessary for the interfacial structure to have no resistance to surface shearing. In SMEDDS, the free energy formed may either be positive or very low or it may even be negative as a result of which spontaneous thermodynamic emulsification takes place [12]. The interface between the continuous aqueous phase and oil is formed on the addition of a binary mixture (non-ionic surfactant/oil) to water. It has been found that self-emulsification takes place due to the penetration of water into the Liquid Crystalline phase that is formed at the water-oil/surfactant interface into which water can penetrate easily, assisted by gentle agitation. After water penetration to a certain limit, it results in the disruption of the interface, and droplet formation takes place.

Phase Diagrams: The microemulsion region is usually characterized by constructing ternary-phase diagrams, as shown in **Fig. 3**. Three components are the basic requirement to form a microemulsion: an oil phase, an aqueous phase, and a surfactant. If a cosurfactant is used, it may sometimes be represented at a fixed ratio to surfactant as a single component, and treated as a single "pseudo-component." The relative amounts of these three components can be represented in a ternary phase diagram. Gibbs phase diagrams can be used to show the influence of changes in the volume fractions of the different phases on the phase behavior of the system. The three components composing the system are each found at an apex of the triangle, where their corresponding volume fraction is 100%. Moving away from that corner reduces the volume fraction of that specific component and increases the volume fraction of one or both of the two other components. Each point within the triangle represents a possible composition of a mixture of the three components or pseudo-components, which may consist (ideally, according to the Gibbs' phase rule) of one, two, or three phases. These points combine to form regions with boundaries between them, which represent the "phase behavior" of the system at constant temperature and pressure [13].

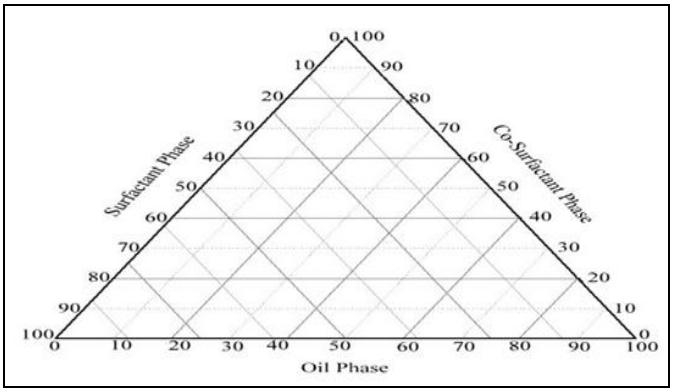

FIG. 3: PSEUDOTERNARY PHASE DIAGRAM

Factors Influencing SMEDDS Formulation: Different factors affecting SMEDDS formulations are discussed as follows:

Nature and Dosage of Drug: For the preparation of high-dose formulations into SMEDDS, they need to have good solubility in at least one of the components of the formulation. Drugs having inadequate solubility (typically with log P values of approximately 2) in lipids are most difficult to be delivered by SMEDDS. The ability of SMEDDS to maintain the drug in solubilized form is greatly influenced by the solubility of the drug in the oil phase. As mentioned above, if surfactant or co-surfactant is contributing to a greater extent in drug solubilization, then there could be a risk of precipitation, as a dilution of SMEDDS will lead to the lowering of the solvent capacity of the surfactant or co-surfactant [14].

Polarity of the Lipophilic Phase: It affects the drug release from emulsion or SMEDDS. The polarity of droplet depends on HLB value, degree of unsaturation and chain length of Fatty Acids, and molecular weight of micronized Fatty Acids and the concentration of emulsifier. The polarity reflects the affinity of the drug for oil and/or water, and the type of forces formed. The high polarity will promote a rapid rate of release of the drug into the aqueous phase. The highest release was obtained with the formulation that had the oil phase with the highest polarity [8].

Charge on Droplet of Emulsion: Many physiological studies show that the potential of

absorptive cells and all other cells in the body are negatively (−ve) charged with respect to mucosal solution in the lumen. A charge may be positive in some formulations.

Equilibrium Solubility Measurement: It is done to determine the possible causes of precipitate formation in the gut. Pouton's study found that formulation in which crystallization occurs may take 5 days to attain equilibrium, and drug can continue to be in a supersaturated state for 1 day (24 h) after the early emulsification process [9, 12.]

Formulation of SMEDDS:

Lipids/Oils: The oil represents one of the most important excipients in the SMEDDS formulation not only because it can solubilize marked amounts of the lipophilic drug or facilitate self-emulsification but also and mainly because it can increase the fraction of lipophilic drug transported *via* the intestinal lymphatic system, thereby increasing absorption from the GI tract depending on the molecular nature of the triglycerides [15, 16].

Both long and medium-chain triglyceride oils with different degrees of saturation have been used for the design of self-emulsifying formulations [17].

Surfactants: The surface-active agents are amphiphilic by nature, the usual surfactant concentration in self-emulsifying formulations required to form and maintain an emulsion state in the GI tract ranged from 30 to 60% w/w of the formulation. The most widely recommended ones being the non-ionic surfactants with a relatively high (HLB) hydrophilic-lipophilic balance [18, 19, 20].

Co-solvents: Co-solvents such as ethanol, propylene glycol (PG), and polyethylene glycol (PEG) are suitable for oral delivery, and they enable the dissolution of large quantities of either the hydrophilic surfactant or the drug in the lipid base.

Additives: Lipid-soluble antioxidants such as α-tocopherol, β-carotene, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA) or propyl gallate could potentially be included in formulations to protect either unsaturated fatty acid chains or drugs from oxidation.

Examples of surfactants, co-surfactants, and co-solvents used in commercial lipid base formulations are presented in **Table 3**.

TABLE 3: COMPONENTS OF SMEDDS [21]

S. no.	Trade name	Chemical name	HLB	Regulatory status
		Lipids		
1	Vegetable oil	Long- chain TAG	-	Oral product, GRAS, FDA IIG
2	Miglyol 812	Medium-chain TAG caprylic/capric TAG	-	Oral product, GRAS, FDA IIG
3	Trcaprylin	Medium-chain TAG	-	-
4	Labrafac CC	caprylic/capric TG	-	-
5	Ethyl oleate	Ethyl ester of C18:1 omega FA	-	FDA IIG
6	Captex 355	Glyceryl caprylatecaprate	-	GRAS, FDA IIG
7	Isopropyl myristate	FA ester	-	FDA IIG
8	Labrafac PG	PG dicaprylocaprate	-	USFA, JSFA, EP
9	Peceol	Glyceryl mono-oleate	3.3	GRAS, E471, EP, USP-NF, FDA IIG
10	Maisine 35-1	Glyceryl mono-linoleate	4	Oral product, GRAS, E471, EP, USP-NF
11	Imwitor 988	Caprylic/capric glycerides	3.8	USP, Ph.Eur
12	Akoline MCM	Caprylic/capric glycerides	5-6	-
		Surfactants		
1	Tween 85	Polyethylene (20) sorbitantrioleate	11	UK
2	Labrafil M1944CS	Oleoylmacrogolglycerides	4	EP, FDA IIG, USP NF
3	Labrafil M2125CS	Linoleoylmacrogolglycerides	4	EP, FDA IIG, USP NF
4	Lauroglycol 90	PG monolaurate	5	USFA, FCC, EFA, USP-NF
5	Vitamin Polysorbate 20/ Tween 20E TPGS	D-alpha-tocopheryl PEG 1000 succinate	13	Oral product
6	Cremophor EL	Polyoxyl 35 castor oil	12-14	Oral product, USP-NF, FDA IIG
7	Gelucire 44/14	Lauroylmacrogolglycerides	14	EP, USP-NF, FDA IIG
8	Labrasol	Capylocaproylmacrogol glycerides	14	EP, USP-NF, FDA IIG
10	Polysorbate 80/ Tween 80	Polyoxyehylene (20) sorbitonmonoleate	15	Oral product, GRAS, EP, USP-NF, FDA IIG
11	Polyoxyehylene (20) sorbitonmonolaurate		16.7	Oral product, GRAS, EP, USP-NF, FDA IIG

Cosurfactants				
S. no.	**Trade name**	**Chemical name**	**HLB**	**Regulatory status**
1	Ethanol	-	-	Oral product, EP, USP-NF
2	PEG	PEG 300 and PEG 400	-	Oral product, EP, USP-NF
3	Transcutol P	Diethylene glycol monoethyl ether	-	EP, FDA IIG

PG, Polyethylene Glycol; PG, Propylene Glycol; MAG, 2-Monoacylglyceride; DAG, Diacylglyceride; FA, Fatty Acid; GRAS, Generally Recognized As Safe; E471, European Food Additives; EP, European Pharmacopoeia; USP-NF, United States Pharmacopoeia-National Formulary; FDA IIG, FDA Inactive Ingredient Guide; Ph.Eur., Pharmacopoeia Europea; USFA, United States Food Administration; FCC, Food Chemicals Codex; JSFA, Japanese Standards for Food Additives; UK, United Kingdom

Characterization of SMEDDS: [22-29] The various ways to characterize SMEDDS are compiled below.

Turbidity Measurement: This identifies efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time. These measurements are carried out on turbidity meters, most commonly the Hach turbidity meter and the Orbeco-Helle turbidity meter.

Droplet Size: This is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release, as well as the absorption and stability of the emulsion. Photon correlation spectroscopy, Freeze-fracture electron microscopy or a Coulter nano-sizer are mainly used for the determination of the emulsion droplet size.

Photon correlation spectroscopy (PCS) is a useful method for the determination of emulsion droplet size, especially when the emulsion properties do not change upon infinite aqueous dilution. PCS analyses the fluctuations in light scattering due to the Brownian motion of the particles using a zeta sizer able to measure sizes between 10 and 5000 nm. Light scattering is monitored at 25°C at a 90° angle, after external standardization with spherical polystyrene beads [43]. However, microscopic techniques should be employed at relatively low dilutions for accurate droplet size evaluation.

Zeta Potential Measurement: This is used to identify the charge of the droplets. In conventional SMEDDS, the charge on an oil droplet is negative because of the presence of free fatty acids; however, incorporation of a cationic lipid, such as oleylamine at a concentration range of 1.0-3%, will yield cationic SMEDDS. Thus, such systems have a positive n-potential value of about 35-45 mV. This positive n-potential value is preserved following the incorporation of the drug compounds.

Determination of Emulsification Time: The process of self-emulsification was observed using light microscopy. The mechanism of emulsification involved erosion of a fine cloud of small particles from the surface of large droplets, rather than a progressive reduction in droplet size.

Liquefaction Time: This test is designed to estimate the time required by solid SMEDDS to melt *in-vivo* in the absence of agitation to simulated GI conditions.

Droplet Polarity: Emulsion droplet polarity is also a very important factor in characterizing emulsification efficiency. The HLB, chain length, and degree of unsaturation of the fatty acid, molecular weight of the hydrophilic portion, and concentration of the emulsifier have an impact on the polarity of the oil droplets. The polarity of the oil droplets is also estimated by the oil/water partition coefficient of the lipophilic drug. Rapid release of the drug into the aqueous phase is promoted by polarity.

Small-Angle X-ray Scattering: This technique can be used to obtain information on the size and shape of the droplets. Small-angle X-ray scattering is capable of delivering structural information of macromolecules between 5 and 25 nm, of repeat distances in partially ordered systems of up to 150 nm. It is used for the determination of the microscale or nanoscale structure of particle systems in terms of such parameters as averaged particle sizes, shapes, distribution, and surface-to-volume ratio.

Drug Precipitation/Stability on Dilution: The ability of SMEDDS to maintain the drug in solubilized form is greatly influenced by the solubility of the drug in the oil phase. If the surfactant or co-surfactant is contributing to the greater extent in drug solubilization, then there could be a risk of precipitation, as a dilution of

SMEDDS will lead to lowering of solvent capacity of the surfactant or co-surfactant; hence it is very important to determine the stability of the system after dilution. This is usually done by diluting a single dose of SMEDDS in 250ml of0.1N HCl solution. This solution is observed for drug precipitation if any. Ideally, SMEDDS should keep the drug solubilized for four to six hours, assuming the gastric retention time of two hours.

Evaluation of SMEDDS:

Thermodynamic Stability Studies: The physical stability of a lipid-based formulation is also crucial to its performance, which can be adversely affected by precipitation of the drug in the excipient matrix. In addition, poor formulation of physical stability can lead to phase separation of the excipient, affecting not only formulation performance, but visual appearance as well. Furthermore, incompatibilities between the formulation and the gelatin capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug [30].

- ✓ **Heating Cooling Cycle:** Six cycles between refrigerator temperature (4ºC) and 45 ºC with storage at each temperature of not less than 48 h is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.

- ✓ **Centrifugation:** Passed formulations are centrifuged thaw cycles between 21 ºC and +25 ºC with storage at each temperature for not less than 48 h is done at 3500 rpm for 30 min. Those formulations that do not show any phase separation are taken for the freeze-thaw stress test.

- ✓ **Freeze-Thaw Cycle:** Three freezes for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking.

Dispersibility Test: The efficiency is assessed using a standard USP XXII dissolution apparatus 2. One mL of each formulation was added to 500 mL of water at 37 ± 0.5 ºC. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The *in-vitro* performance of the formulations is visually assessed using the following grading system.

Grade A: Rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance.

Grade B: Rapidly forming, slightly less clear emulsion, having a bluish-white appearance.

Grade C: Fine milky emulsion that forms within 2 min.

Grade D: Dull, grayish-white emulsion having a slightly oily appearance that is slow to emulsify (longer than 2 min).

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT. While formulation falling in Grade C could be recommended for SMEDDS formulation.

Turbidimetric Evaluation: Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. A fixed quantity of self-emulsifying system is added to a fixed quantity of suitable medium (0.1N hydrochloric acid) under continuous stirring (50 rpm) on the magnetic plate at ambient temperature, and the increase in turbidity is measured using a turbidimeter. However, since the time required for complete emulsification is too short, it isn't possible to monitor the rate of change of turbidity.

Viscosity Determination: The SMEDDS system is generally administered in soft gelatin or hard gelatin capsules. So, it can be easily pourable into capsules, and such a system should not be too thick to create a problem. The rheological properties of the microemulsion are evaluated by Brookfield viscometer.

Refractive Index and Percent Transmittance: Refractive index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by a refractometer by placing a drop of solution on the slide, and it compares with water (Refractive index of water 1.333). The percent transmittance of the system is measured at a particular wavelength using UV-spectrophotometer, keeping distilled water as blank. If the refractive index of the system is similar to the refractive index of water and

formulation have percent transmittance > 99%, then formulation has transparent nature.

Electro Conductivity Study: The SMEDD system contains an ionic or non-ionic surfactant, oil, and water. So, this test is used to measure the electroconductive nature of the system. The electroconductivity of the resultant system is measured by electroconductometer.

***In-vitro* Diffusion Study:** *In-vitro* diffusion studies are performed to study the release behavior of formulation from the liquid crystalline phase around the droplet using the dialysis technique.

Drug Content: Drug from pre-weighed SMEDDS is extracted by dissolving in a suitable solvent. The drug content in the solvent extract was analyzed by a suitable analytical method against the standard solvent solution of the drug.

Yield of the SMEDDS: The SMEDDS formed is filtered from the solvent, dried in the desiccators and weighed to get the yield of the SMEDDS formulated per batch. Percentage yield can be calculated by the formula.

$$\% \text{ recovery} = W1 / W2 + W3 \times 100 \ldots\ldots(1)$$

Where, W1 is the weight of the SMEDDS formulated, W2 weight of the drug added, W3 is the weight of the lipid and surfactant used as the starting material.

Applications of SMEDDS:

Improvement in Solubility and Bioavailability: Multifold increase in bioavailability of BCS class-II drugs by improving the solubility and dissolution rate of the drugs. In SEDDS, the lipid matrix interacts readily with water, forming a fine particulate Oil-in-water (o/w) emulsion. The emulsion droplets will deliver the drug to the gastrointestinal mucosa in the dissolved state readily accessible for absorption. Therefore, the increase in AUC *i.e.,* bioavailability and Cmax is observed with many drugs when presented in SMEDDS.

Protect Drug Against Biodegradation: Many drug formulations are degraded in physiological fluids/ system due to change in the pH around drug. Such as acidic pH in stomach leads to enzymatic or hydrolytic degradation, *etc*. SMEDDS formulation prevents the drug from biodegradation by forming an obstacle among the drug and the degrading environment, which is formed due to a liquid crystalline phase. The ability of self-emulsifying drug delivery system to reduce degradation as well as improve absorption may be especially useful for drugs, for which both low solubility and degradation in the GI tract contribute to a low oral bioavailability [31]. Many drugs are degraded in the physiological system, may be because of acidic PH in the stomach, enzymatic degradation or hydrolyte Such drugs when presented in the form of SEDDS can be well protected against these degradation processes as a liquid crystalline phase in SEDDS might be an act as a barrier between degradation environment and the drug [32].

No Effect of Lipid Digestion Process: This drug delivery system is unaffected from lipolysis because this system is not degraded by the action of pancreatic lipases and bile salts because of these help in self-emulsification of formulation only [33].

Enhance Drug Loading Capacity: Formulation excipients provide high solubility of drug, which results in high drug loading capacity of the formulation.

SMEDDS for Herbal Drugs and Traditional Medicines: A large number of herbal drugs and traditional medicines are being exploited and used for the development of SMEDDS because most of them have volatile and fixed oils [34, 35].

Delivery of Peptides: This drug delivery system provides protection from enzymatic degradation in GIT due to which this system is suitable for the delivery of peptides, hormones, enzyme-substrate/inhibitors.

Controlled Release Formulation: Polymer addition in the composition of SMEDDS provides prolong/control the release of medicament. Different formulation approaches that have been sought to achieve sustained release, increase bioavailability, and decrease the gastric irritation of ketoprofen include the preparation of matrix pellets of nano-crystalline ketoprofen, sustained-release ketoprofen microparticles and floating oral ketoprofen systems and transdermal systems of ketoprofen. Preparation and stabilization of nano-crystalline or improved solubility forms of drug

may pose processing, stability, and economic problems.

This problem can be successfully overcome when Ketoprofen is presented in SMEDDS formulation. This formulation enhanced bioavailability due to the increase in the solubility of the drug and minimizes the gastric irritation [36, 37, 38].

Innovations in SMEDDS

Supersaturable SEDDS (S-SEDDS): The toxic effects of surfactant are well known and by using these surfactants at such a high level in SMEDDS formulations can lead to GI side-effects, thus to overcome this problem a new class of formulations, called as supersaturable SMEDDS formulations, have been designed and developed. Higuchi T. proposed the potential for supersaturated drug formulations for the improvement of drug absorption. Polyvinylpyrrolidone and water-soluble cellulosic polymers such as hydroxypropyl methylcellulose, methylcellulose, and hydroxyl propyl MC phthalate are useful in generating a supersaturatable state with a number of poorly water-soluble drug [39]. The S-SMEDDS approach is to generate a supersaturated solution of the drug when the formulation is released from an appropriate dosage form into an aqueous medium. Surpersaturation is intended to increase the thermodynamic activity to the drug beyond its solubility limit and, therefore, there is an increased driving force for transit into and across the biological barrier. Hydroxypropyl methylcellulose and related cellulose polymers are well recognized for their propensity to inhibit crystallization and maintain the supersaturated state for prolonged time periods.

A supersaturable self-microemulsifying drug delivery system (S-SMEDDS) of paclitaxel was developed employing HPMC as a precipitation inhibitor with a conventional SMEDDS formulation. *In-vitro* dilution of the S-SMEDDS formulation resulted in the formation of a microemulsion, followed by slow crystallization of paclitaxel on standing. This result indicated that the system was supersaturated with respect to crystalline paclitaxel, and the supersaturated state was prolonged by HPMC in the formulation. In the absence of HPMC, the SMEDDS formulation underwent rapid precipitation, yielding a low paclitaxel solution concentration. A pharmaco-kinetic study showed that the paclitaxel S-SMEDDS formulation produced approximately a 10-fold higher maximum concentration (Cmax) and a 5-fold higher oral bioavailability compared with that of the orally administered Taxol formulation [40].

Self-microemulsifying Mouth Dissolving Film (SMMDF): SMMDF was developed by Xiao for water-soluble drugs. Indomethacin was produced by fusing self-microemulsifying segments with a solid carrier like microcrystalline cellulose, low-substituted HPMC, and hypromellose. The SMMDF breaks inside within 20 sec. and discharged medicament completely within 5 min in the disintegration medium with globule size of 28.81 ± 3.26 nm. Cmax and AUC for SMMDF were found to be considerably higher than that of normal mouth dissolving film or tablet, and T-max of SMMDF was found to be essentially diminished. Results concluded that SMMDF is another promising dosage form that has remarkable attributes of accommodation, rapid action, and improved oral bioavailability of a poorly water-soluble drug [41].

Formulations of Lecithin-Linker for SE Delivery of Nutraceuticals: Chu *et al*. studied lecithin-linker microemulsions in which soybean lecithin is blended with lipophilic and hydrophilic linkers. Lecithin-linker creates self-emulsification with β-sitosterol and β-carotene. The grouping of the sorbitanmonooleate (lipophilic linker) was done to reduce the development of fluid precious stones. Grouping of hydrophilic linkers, *i.e.*, PEG-6-caprylic/caprylic glycerides and decaglyceryl-caprate/caprylate, was steadily checked until clear microemulsions were formed [41].

Sponges Carrying SMEDDS: Fabrication of sponges carrying SMEDDS for improving the solubility of lipophilic drugs is a challenging topic nowadays. The nanosponge structures focused on inspecting in electron microscopy and little edge X-pillar diffusing. The mix of sponge and SMEDDS gives a solid structure for SMEDDS that can deal with the use of the delivery of hydrophobic medicament [42].

Herbal SMEDDS: SMEDDS contained fluids are filled in hard gelatin capsules were taken into

consideration for formulating safe and stable dosage forms for herbal extracts. One scientist worked for the solubility enhancement of herbal extract. It comprised of Cremophor RH 40 (40%), Plurol Oleique (30%), and herbal extract (30%) and showed complete discharge in 10 min. SMEDDS also passes the stability testing under storage conditions as per ICH guidelines for 3 months. Thus SMEDDS appeared like an amazing approach to increase the bioavailability and solubility of herbal drugs [43].

Self-Double-Emulsifying Drug Delivery System (SDEDDS): SDEDDS has the ability to instantly emulsify to double emulsions, *i.e.*, water-in-oil-in-water (w/o/w) in the mixed aqueous GI surroundings in which drug is enclosed (encapsulated) in internal phase which is the water of double emulsions. They are used to enhance the oral absorption of a peptide-like drug with relatively high solubility and low permeability [43].

Positively Charged SEDDS: One of the common difficulties faced by scientists in the formulation was to discover the methods for the improvement of oral bioavailability of drugs with poor water solubility. This positively charged SEDDS results in an increase in bioavailability than the SEDDS having a negative charge. Cationic lipids are used in these types of systems [44].

Self-Microemulsifying Floating Dosage Form: Drug having low solubility, undergoes pre-systemic metabolism, and irregular absorption of the drug throughout the GIT and faces low oral bioavailability. The floating system increases the residence time of drugs in the stomach, which results in the prolonged release of the drugs.

The new floating formulation of furosemide prepared by its adsorption onto a blend of excipients, matrix-forming polymers such as HPMC E50 LV and HPMC K4M, and $NaHCO_3$ (a gas-generating agent) to attain a floating matrix with controlled release drug profile [44].

SE Phospholipid Suspension (SEPS): SEPS contains a large amount of phospholipids that help the drug to stay solubilized under *in-vivo* conditions, which is necessary for bioavailability improvement. Phospholipids are endogenous lipids with efficient *in-vivo* emulsification ability. This formulation requires lesser quantity of cosurfactant/ surfactant and thus is comparatively safe and does not cause any serious health complication [45].

Solid SMEDDS (S-SMEDDS): SMEDDS can exist in either liquid or solid states. S-SMEDDS have been extensively exploited in recent years. This novel technology provides an effective alternative to the conventional liquid SMEDDS for drugs having poor solubility. S-SMEDDS is prepared by adding semisolid/ liquid constituents into powders or nanoparticles by using different solidification methods such as spray drying, adsorption onto solid carriers, melt granulation, and melt extrusion techniques.

To some extent, S-SMEDDS are combinations of SMEDDS, and solid dosage forms, so many properties of S-SMEDDS (*e.g.*, excipients selection, specificity, and characterization) are the sum of the corresponding properties of both SMEDDS and solid dosage forms. These can be processed into other solid SE dosage forms such as capsules, solid dispersions, dry emulsions, microspheres, nanoparticles, suppositories, implants, beads, pellets, and tablets.

Advantages of S-SMEDDS: [46]

- Spontaneous formation
- Ease of manufacture and low cost
- Thermodynamic stability and improved solubilization of bioactive materials
- More consistent temporal profiles of drug absorption Greater bioavailability
- Less drug needs to be used
- Faster release rates and improvement of the drug acceptance by consumers
- Selective drug targeting toward a specific absorption window in the GI tract and
- Drug protection from the hostile environment in the gut
- They offer an improvement in the rate and extent of absorption and result in more reproducible blood time profiles
- Lower cost.

Recent Advances in S-SMEDDS: [47-50]

SE Solid Dispersions: These formulations consist of a dispersion of the drug in an inert excipient matrix, but some manufacturing difficulties and

stability problems existed. SE excipients have the ability to improve the absorption of drugs with poor solubility. SE excipients such as Gelucire 50/02, Gelucire 44/14, Transcutol, Labrasol, and tocopheryl PEG 1000 succinate have been used extensively in such preparations. They may also be filled directly into hard gelatin capsule shells in the molten state due to the availability of self-dispersing waxy semisolid excipients. Gelucire 44/14 and Gelucire 50/02 are employed for this purpose because these excipients are semisolid and can be filled directly into the capsules in a liquefied state. Gelucire improves the absorption of the drug due to its high surface activity.

Dry Emulsions: These are the powdered solid dosage forms that instantly get emulsified on the addition of water in the formulation. Dry emulsion formulations are typically prepared from oil/ water emulsions containing a solid carrier like lactose and maltodextrin in the aqueous phase by rotary evaporation, freeze-drying or spray drying. The outcome in this field is the recently formulated enteric-coated dry emulsion preparation of amlodipine with dextrin as a carrier for the transport of peptide and protein drugs orally by Toorisaka and his colleagues. The preparation consisted of vegetable oil, surfactant, and pH-responsive polymer. Myers and Shively developed solid-state glass emulsions. In this method, drug dissolved in vegetable oil is mixed with sucrose solution. Such emulsifiable glasses have the benefit of not needing any surfactants in the formulation. The dry foam was produced by rotator evaporation of mixture under vacuum. Emulsion is produced by addition of this dry foam. Dry emulsion technology solves the stability problems associated with classic emulsions such as phase separation, contamination by a microorganism, etc. during storage and helps also avoid using harmful or toxic organic solvents.

SE Sustained-Release Microspheres: Quasi-emulsion solvent-diffusion process of the spherical crystallization technique was used to prepare sustained-release microspheres of traditional Chinese medicine and zedoary turmeric oil by You *et al*. This Chinese medicine has potent pharmacological activity including tumor suppressive, antibacterial, and antithrombotic. The microspheres were prepared using HPMC acetate succinate and aerosil 200. After oral administration of such microspheres to rabbit's plasma, concentration-time profiles were attained with resulting bioavailability of 135.6% with respect to the conventional liquid SEDDS.

Self-Nanoemulsifying Drug Delivery System/SE Nanoparticles: Techniques used in the production of SE nanoparticles are solvent injection technique, sonication, and emulsion-diffusion-evaporation. In the solvent injection technique, lipids, drugs, and surfactants are all liquefied together and added drop by drop into the agitated non-solvent. The final SE nanoparticles were strained and dried completely. In other studies, drug and excipients were melted all together and introduced into a solution of non-solvent. Nanoparticles were then separated by centrifugation and lyophilization.

SE Implants: Loomis invented copolymers having a bioresorbable region, a hydrophilic region, and at least two cross-linkable functional groups per polymer chain that showed SE properties without incorporating the emulsifying agent. These copolymers can be used as good sealants for implantable prostheses.

Self-micron Emulsifying Sustained/Controlled-Release Tablets: Combinations of lipids and surfactants have presented the great potential of producing SME tablets. In order to reduce the amount of solidifying excipients required for the transformation of SEDDS into solid dosage forms, a gelled SMEDDS has been developed, colloidal silicon dioxide (Aerosil 200) was selected as a gelling agent for the oil-based systems, which gives the advantage of reducing the amount of required solidifying excipients and aiding in slowing down of the drug release. SE tablets may increase their penetration efficacy through the GI mucosal membranes, potentially reducing GI bleeding. The resultant SME tablets consistently maintained a higher active ingredient concentration in blood plasma over the same time frame compared with a non-emulsifying tablet. The newest advance in the research field of SME tablet is the SME osmotic pump tablet, where the elementary osmotic pump system was chosen as the carrier of SMES. This system has extraordinary features such as stable plasma concentrations and controllable drug release rate, allowing a bioavailability of 156.78% relative to commercial carvedilol tablets.

Self-emulsifying Beads: Patil and Paradkar investigated porous polystyrene beads for delivering SEFs using the solvent evaporation method. They are inert and stable over a wide range of pH and extreme conditions of humidity and temperature. Copolymerization of styrene and divinylbenz of pores of PPB affected the loading efficiency and *in-vitro* release of drugs from Self Emulsifying system filled with Polystyrene beads.

SE-Controlled/Sustained Release Pellets: Pellets are dosage forms with advantages of ease of manufacturing, reduced inter- and intra-subject irregularities of plasma profiles, and minimized irritation of GIT without affecting the bioavailability of the drug. Serratoni *et al*., formulated self-emulsifying controlled release pellets by adding drugs into SE system with improved drug release and then covering it with a water-insoluble polymer that reduced the release rate of the drug. Spherical pellets were prepared by extrusion/spheronization with low friability that has two water-insoluble model drugs (methyl and propyl parabens), and system contains mono-di-glycerides and polysorbate 80.

Self-emulsifying Capsules: Poorly water-soluble drugs can be dissolved in SEDDS and encapsulated in hard or soft gelatin capsules to produce convenient single unit dosage forms. Administration of capsules containing conventional liquid SE formulations, microemulsion droplets form and subsequently disperse in the GI tract to reach sites of absorption. However, if irreversible phase separation of the microemulsion occurs, an improvement of drug absorption cannot be expected. For handling this problem, sodium dodecyl sulfate was added to the SE formulation. With a similar purpose, the supersaturable SEDDS was designed, using a small quantity of HPMC (or other polymers) in the formulation to prevent precipitation of the drug by generating and maintaining a supersaturated state in vivo. This system contains a reduced amount of a surfactant, thereby minimizing GI side effects. Oral administration of SME capsules has been found to enhance patient compliance compared with the previously used parenteral route. For that, low molecular weight heparin (LMWH) used for the treatment of venous thromboembolism was clinically available only *via* the parenteral route. So, oral LMWH therapy was investigated by formulating it in hard capsules. LMWH was dispersed in SMEDDS, and thereafter the mixture was solidified to powders using three kinds of adsorbents: microporous calcium silicate, magnesium aluminum silicate, and silicon dioxide. Eventually, these solids were filled into hard capsules.

TABLE 4: MARKETED FORMULATIONS [51]

S. no.	Active moiety	Trade name	Mfg. Company	Dosage forms	Indication
1	Tretinoin	Vesanoid	Roche	Soft gelatin capsule, 10 mg	Acute promyelocytic leukemia
2	Isotretinoin	Accutane	Roche	Soft gelatin capsule, 10, 20 and 40 mg	Acne
3	Cyclosporine	Panimumbioral	Panacea Biotec	Capsule, 50 and 100 mg	Immunosuppressant
4	Cyclosporin A	Gengraf	Abbott	Hard gelatin capsule, 25 and 100 mg	Immunosuppressant
5	Cyclosporin A	Sandimmune	Novartis	Soft gelatin capsule, 25, 50 and 100 mg	Immunosuppressant
6	Lopinavir and Ritonavir	Kaletra	Abbott	Soft gelatin capsule, Lopinavir 133.33 mg and Ritonavir 33.3 mg	HIV antiviral
7	Sanquinavir	Fortovase (Roche)		Soft gelatin capsule, 200 mg	HIV antiviral
8	Tipranavir	Aptivus	BoehringerIngelheim	Soft gelatin capsule, 250 mg	HIV antiviral
9	Amprenavir	Agenerase	GlaxoSmithKline	Soft gelatin capsule	HIV antiviral
10	Ritonavir	Norvir	Abott laboratories	Soft gelatin capsules	HIV antiviral
11	Cyclosporin	Neoral	Novartis	Soft gelatin capsules, 25and 100 mg	Immunosuppressant
12	Fenofibrate	Lipired	Square Pharmaceuticals Ltd.	Hard gelatin capsules, 200mg	Lowering of TG level
13	Valproic acid	Convule	Opsonin Pharma limited	Soft gelatin capsules, 100 and 200 mg	Antiepileptic

CONCLUSION: SMEDDS are a promising approach for the formulation of drugs with poor aqueous solubility. The development of SMEDDS could be an effective way to overcome the issue of solubility of drugs with relatively lesser solubility in the fluids of GIT. The oral delivery of hydrophobic drugs can be made possible by SMEDDS, which has been shown to substantially

improve oral bioavailability. As improvements or alternatives of conventional liquid SMEDDS, S-SMEDDS are superior in reducing production cost, simplifying industrial manufacture, and improving stability as well as patient compliance. As mentioned above, numerous studies have confirmed that S-SMEDDS substantially improved solubility/dissolution, absorption, and bioavailability of poorly water-soluble drugs. Most importantly, S-SMEDDS are very flexible in developing various solid dosage forms for oral and parenteral administration. Besides that, GI irritation is also reduced and controlled/sustained release of drug is achievable. SMEDDS can overcome the limitations of marketing the many drugs in the future. Still, a long way has to be covered before launching more SMEDDS products in the market because SMEDDS needs further exploitation, including researches about bioavailability and development of *in-vitro*, *in-vivo* correlation (IVIVC) and other dosage forms.

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