Self-emulsifying drug delivery systems (SEDDS) have gained exposure for their ability to increase solubility and bioavailability of poorly soluble drugs (Sachin et al. 2010). SEDDS are isotropic mixtures of oils and surfactants, sometimes containing cosolvents, and can be used for the design of formulations in order to improve the oral absorption of highly lipophilic compounds. About 40% of the drug candidates identified via combinatorial screening programs are poorly water soluble. The aqueous solubility of poorly water soluble drugs is usually less than 100 μg/ml (Ngik, Amal et al. 2011). Especially poorly soluble, highly permeable active pharmaceutical ingredients (BCS Class II drugs) represent a technological challenge, as their poor bioavailability is solely caused by poor water solubility resulting in low drug absorption (Hentzchel, 2011).

Different techniques have been reported in the literature to achieve better drug dissolution rates. For example,

(a) Reduce the particle size via micronization or nanonization to increase the surface area,
(b) Co-grinding,
(c) Formulation of inclusion complexes,
(d) Solubilisation by surfactants,
(e) Solid dispersions,
(f) Inclusion of the drug solution or liquid drug into soft gelatin capsules such as self-emulsifying drug delivery systems (Vijay et al. 2011). Recently, SEDDS have been formulated using medium chain tri-glyceride oils and non-ionic surfactants, the latter being less toxic. Upon peroral administration, self-emulsifying formulations distribute readily in the GI tract, and the digestive motility of the stomach and the intestines provides sufficient agitation enough for the spontaneous formation of emulsions. In the case of sparingly soluble drugs that exhibit dissolution rate limited absorption, the SEDDS offer a way to improve the rate and extent of oral absorption and to produce more reproducible blood time profiles.
To improve dissolution/solubility and oral bioavailability of a formulation one of the approaches is self dispersing lipid formulations (SDLF’s) (Pouton, 1992). SDLFs, surfactant dispersions, solid lipid nanoparticles, liposomes, emulsions and oils are various lipid based formulations. There are two types of SDLFs which includes Self-Emulsifying Drug Delivery Systems (SEDDS) and Self-Micro Emulsifying Drug Delivery Systems (Pouton, 2000).

1.1 ADVANTAGES OF SEDDS: (Patel et al. 2008)

- It acts as a substitute for traditional oral formulations of lipophilic drugs.
- It enhances the dissolution rate and hence, bioavailability of hydrophobic drugs.
- It provides better consistent temporal profiles of drug absorption.
- It helps in selective drug targeting toward a specific site in the GI tract.
- It protects drug molecule from the hostile environment of GIT.
- More consistent temporal profiles of drug absorption,
- Selective targeting of drug(s) toward specific absorption window in GIT
- Protection of drug(s) from the hostile environment in gut.
- Control of delivery profiles
- Reduced variability, including food effects
- Protection of sensitive drug substances.

Table 1.1: Problems of BCS class entities that can be solved through SEDDS

<table>
<thead>
<tr>
<th>BCS Class</th>
<th>Description</th>
<th>Problems that can be solved through SEDDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>High solubility, High permeability</td>
<td>Enzymatic degradation, gut wall efflux</td>
</tr>
<tr>
<td>Class II</td>
<td>Low solubility, High permeability</td>
<td>Solubilization and bioavailability</td>
</tr>
<tr>
<td>Class III</td>
<td>High solubility, Low permeability</td>
<td>Enzymatic degradation, gut wall efflux, Bioavailability</td>
</tr>
<tr>
<td>Class IV</td>
<td>Low solubility, Low permeability</td>
<td>Solubilization, enzymatic degradation, gut wall efflux and bioavailability</td>
</tr>
</tbody>
</table>

1.2 Lipid formulation classification system

In 2000, Lipid Formulation Classification System was introduced, and later in 2006, an extra ‘type’ of formulation was added. The rationale behind this system was to facilitate interpretation of in vivo studies and enable selection of most suitable formulation depending on the physico-chemical properties of the drug (Pouton, 2000; 2006).
1.2 indicates the fundamental differences between types I, II, III and IV formulations (Pouton, 2008).

### Table 1.2. Lipid formulation classification system by Pouton composition (%)

<table>
<thead>
<tr>
<th>Classes</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycerides (mono-,di-, tri-glycerides)</td>
<td>100</td>
<td>40–80</td>
<td>40–80</td>
<td>&lt; 20</td>
<td>0</td>
</tr>
<tr>
<td>Lipophilic surfactants (HLB &lt; 12)</td>
<td>0</td>
<td>20–60</td>
<td>20–40</td>
<td>0</td>
<td>0–20</td>
</tr>
<tr>
<td>Hydrophilic surfactants (HLB &gt; 12)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>20–50</td>
<td>20–80</td>
</tr>
<tr>
<td>Co-solvents</td>
<td>0</td>
<td>0</td>
<td>0–40</td>
<td>20–50</td>
<td>0–80</td>
</tr>
</tbody>
</table>

Type I formulations comprise formulations solubilized drug in triglycerides and/or mixed glycerides or in an oil-in-water emulsion stabilized by low concentration of emulsifiers. These systems show poor initial aqueous dispersion and require digestion by pancreatic lipase / collapse in the GIT to produce more amphiphilic lipid digestion products and promote drug transfer into the colloidal aqueous phase. Type I formulations therefore are a good option for drugs having sufficient solubility in oils. Valproic acid has been formulated in soft gelatin capsule containing corn oil as lipidic component.

Type II formulations are referred to as SEDDS. SEDDS are isotropic mixtures of lipids and lipophilic surfactants (HLB <12), co-surfactant and the drug. They form oil-in-water emulsions under mild agitation following dilution with aqueous phases. Self emulsification is generally obtained at surfactants contents above 25% w/w. But at a higher surfactants concentration (greater than 50-60%) (w/w)), the progress of emulsification may be hindered by the formation of viscous crystalline gels at the oil / water interface. No Type II formulation has been marketed till date.

Type III formulations are commonly referred as self-microemulsifying drug delivery systems (SMEDDS). They comprise of oils, hydrophilic surfactants (HLB>12) and co-solvents such as ethanol, propylene glycol and polyethylene glycol. Type III formulations are further divided into Type IIIA and Type IIIB formulations. Later include higher amount of hydrophilic surfactants and co-solvents and lesser lipid content as compared to Type IIIA. Type IIIB formulations pose greater risk of drug precipitation on dispersions given their high content of hydrophilic surfactants and co-solvents. The distinction between SEDDS (Type II) and SMEDDS (Type III)
formulations is commonly made on the globule size and optical clarity of the resultant dispersion. SEDDS formulations form opaque dispersions with globule sizes > 100nm whereas SMEDDS disperse to give optically clear or slightly opalescent dispersions with globule sizes < 100nm. An example of marketed Type III formulation is Neoral (Novartis) cyclosporine formulation. This formulation comprised of corn oil glycerides, cremphor RH40, glycerol, propylene glycol and ethanol.

Type IV category was added to the LFCS by Pouton in 2006. Type IV formulations are devoid of oils and represent the most hydrophilic formulations. They produce fine dispersions when introduced to aqueous media. A type IV formulation is useful for drugs which are hydrophobic but not lipophilic. An example of a commercial type IV formulation is Agenerase (GlaxoSmithKline), a capsule formulation of the HIV protease inhibitor amprenavir containing tocopherol polyethylene glycosuccinate (TPGS) as a surfactant and PEG 400 and propylene glycol as co-solvent.

Self-Nano emulsifying Drug Delivery System having size range of globules is less than 100nm under dispersion of water.

1.3 Construction of Pseudo ternary phase diagram (Latika et al., 2013)

The number and types of phases, the percentage weight of each phase and the composition of each phase at a particular temperature and composition of the system can be determined by the ternary phase diagram. Usually these diagrams are three dimensional, but it can be illustrated in two dimensions for ease of drawing and interpretation (Patel and Vavia, 2005). On further incorporation of water, there occurs a correlation between emulsification efficiency and region of enhanced water solubilization and phase inversion region, formation of lamellar liquid crystalline dispersion phase. With the help of the equilibrium phase diagram, the comparison of different surfactant and their synergy with co-surfactant can be determined. For three component systems, phase behavior can be represented by a ternary phase diagram.

Ternary phase diagram is useful to identify best emulsification regions of Oil, Surfactant and Co-Surfactant combinations. The methods used to plot Ternary phase diagrams are namely Dilution method and Water Titration method.
1.3.1 Water Titration Method

The pseudo-ternary phase diagrams were also constructed by titration of homogenous liquid mixtures of oil, surfactant and co-surfactant with water at room temperature. Oil phase, Surfactant and the co-surfactant (surfactant: co-surfactant ratio) were prepared in ratios varying from 9:1 to 1:9 and weighed in the same screw-cap glass tubes and were vortexed. Each mixture was then slowly titrated with aliquots of distilled water and stirred at room temperature to attain equilibrium. The mixture was visually examined for transparency. After equilibrium was reached, the mixtures were further titrated with aliquots of distilled water until they showed the turbidity. Clear and isotropic samples were deemed to be within the microemulsion region. No attempts were made to completely identify the other regions of the phase diagrams. Based on the results, the appropriate percentage of oil, surfactant and co-surfactant was selected, correlated in the phase diagram and were used for preparation of SEDDS.

Example of Phase Diagram

![Phase Diagram](image)

**Fig. 1.1 : Mechanism of self emulsification (Latika et al. 2013)**

In emulsification process the free energy ($\Delta G$) associated is given by the equation:

$$\Delta G = \Sigma N_i \pi r^2 \sigma$$

In which “N” is number of droplets with radius “r” and “$\sigma$” is interfacial energy. It is apparent from equation that the spontaneous formation of the interface between the oil and water phase is energetically not favored. The system commonly classified as SEDDS has not yet been shown to emulsify spontaneously in the thermodynamic sense. The process of self-emulsification was observed using light microscopy.
Chapter-I

Introduction

The emulsification process may be associated with the ease with water penetrates the oil-water interface with the formation of liquid crystalline phases resulting in swelling at the interface thereby resulting in greater ease of emulsification.

1.4 Composition of SEDDS

The self-emulsifying process depends on:

- The nature of the oil and surfactant
- The concentration of surfactant
- The temperature at which self-emulsification occurs.

Drugs

Generally, SEDDS are prepared for drugs possessing poor water-solubility. BCS class II drugs are usually employed in preparation of SEDDS. Examples of drugs which belong to BCS class II include itraconazole, nifedipine, vitamin E, simvastatin, danazol, ketoconazole, mefanimic acid, carbamazepine, glibenclamide, cyclosporine-A, ritonavir etc. (Shobith et al. 2012).

Surfactant

Numerous compounds exhibiting surfactant properties might be working in the design of self-emulsifying systems, but the choice is limited at the same time as very few surfactants are orally suitable, because safety is a major determining factor in choosing a surfactant. Emulsifiers of natural origin are preferred since they are considered to be safer than the synthetic surfactant. The most extensively suggested ones being the non-ionic surfactants with a relatively high hydrophilic lipophilic balance (HLB). The role of surfactant is to enhance the absorption of the drug, because of induction of permeation changes in biological membrane. It is reported that a cationic emulsion shows greater absorption than an anionic emulsion. To form stable SEDDS, 30-60% concentration of surfactant is used (Khamkar et al. 2011).

Oils

Long chain triglyceride and medium chain triglyceride oils with different degree of saturation have been used in the design of SEDDS. Unmodified edible oils provide the most natural basis for lipid vehicles, but their poor ability to dissolve large amounts of hydrophobic drugs and their relative difficulty in efficient self emulsification markedly reduces their use in SEDDS. Recently medium chain triglycerides are replaced by novel
semi synthetic medium chain triglycerides such as gelucire, other suitable oil phases are
digestible or non-digestible oils and fats such as olive oil, corn oil, soya bean oil, palm
oil and animal fats (Khamkar et al. 2011).

Co-solvents
Usually an effective self emulsifying formulation requires a high concentration of
surfactant. Accordingly, co-solvents such as ethanol, propylene glycol and polyethylene
glycol are required to facilitate the dissolution of large quantities of hydrophilic
surfactant. These co-solvents sometimes play the role of the co-surfactant in the micro-
emulsion system. On the other hand, alcohol and other volatile co-solvents have the
drawback of evaporating into the shell of soft or hard gelatin capsules, leading to
precipitation of the drug (Roshan & Karan 2012).

Polymers
Inert polymer matrix representing from 5 to 40% of composition relative to the weight,
which is not ionizable at physiological pH and being capable of forming matrix are
used. Examples are hydroxyl propyl methyl cellulose, ethyl cellulose, etc. (Khamkar
etal. 2011).

Table -1.3 Type of surfactants used with drugs in SEDDS (PA Patel et al. 2008)

<table>
<thead>
<tr>
<th>Surfactant</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tween 80</td>
<td>Ibuprofen (Obitte NC et al. 2010)</td>
</tr>
<tr>
<td>PEG-35</td>
<td>Cyclosporine-A (Zhao et al. 2011)</td>
</tr>
<tr>
<td>Cremophore EL</td>
<td>Furosemide (Ashish et al. 2010)</td>
</tr>
<tr>
<td>Cremophore RH 40</td>
<td>Glibenclamide (Maria S et al 2013)</td>
</tr>
<tr>
<td>Tween 80,Tween 20</td>
<td>Diclofenac sodium (Gajendra et al. 2012)</td>
</tr>
</tbody>
</table>
Table – 1.4 : Type of surfactants used in marketed SEDDS: (PA Patel et al. 2008)

<table>
<thead>
<tr>
<th>Surfactant</th>
<th>Marketed Product</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cremophor RH 40</td>
<td>Neoral soft Gelatin capsule</td>
<td>Cyclosporine A</td>
</tr>
<tr>
<td>Span 20</td>
<td>Kaletra tablet, soft gelatin capsule</td>
<td>Lopinavir</td>
</tr>
<tr>
<td>Gelucire 44/14</td>
<td>Lipofen hard Gelatin capsule</td>
<td>Fenofibrate</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>Targretin soft gelatin capsule</td>
<td>Bexarotene</td>
</tr>
</tbody>
</table>

Table -1.5 : Type of oil used with drug in SEDDS

<table>
<thead>
<tr>
<th>Oil</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palm kernel oil</td>
<td>Ibuprofen (Obitte NC et al. 2010)</td>
</tr>
<tr>
<td>Castor oil</td>
<td>Cyclosporin-A (Zhao et al. 2011)</td>
</tr>
<tr>
<td>Captex 500</td>
<td>Furosemide (Ashish et al. 2010)</td>
</tr>
<tr>
<td>Capmul MCM C8</td>
<td>Glibenclamide (Maria S et al 2013)</td>
</tr>
<tr>
<td>Lemon oil</td>
<td>Diclofenac Sodium (Gajendra et al. 2012)</td>
</tr>
</tbody>
</table>

Table -1.6 : Type of oil used in marketed preparation: (PA Patel et al. 2008)

<table>
<thead>
<tr>
<th>Oil</th>
<th>Marketed product</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corn oil</td>
<td>Sandimmune soft gelatin capsule</td>
<td>Cyclosporine A</td>
</tr>
<tr>
<td>PeppermintOil</td>
<td>Kaletra oral Solutions</td>
<td>Lopinavir</td>
</tr>
<tr>
<td>Sesame oil</td>
<td>Marinol soft gelatin Capsule</td>
<td>Dronabinol</td>
</tr>
<tr>
<td>Peanut oil</td>
<td>Prometrium soft gelatin capsule</td>
<td>Progesterone</td>
</tr>
</tbody>
</table>
### Table 1.7: Example of surfactants, co-surfactant, and co-solvent used in commercial formulations (Patel et al. 2008)

<table>
<thead>
<tr>
<th>Excipient Name (commercial name)</th>
<th>Examples of commercial products in which it has been used</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surfactants/co-surfactants</strong></td>
<td></td>
</tr>
<tr>
<td>Polysorbate 20 ( Tween 20)</td>
<td>Targretin soft gelatin capsule</td>
</tr>
<tr>
<td>Polysorbate 80 ( Tween 80)</td>
<td>Gengraf hard gelatin capsule</td>
</tr>
<tr>
<td>Sorbitan monooleate (Span 80)</td>
<td>Gengraf hard gelatin capsule</td>
</tr>
<tr>
<td>Polyoxy-35-castor oil (Cremophor RH40)</td>
<td>Gengraf hard gelatin capsule, Ritonavir soft gelatin capsule</td>
</tr>
<tr>
<td>Polyoxy-40- hydrogenated castor oil (Cremophor RH40)</td>
<td>Neoral soft gelatin capsule, Ritonavir oral solution</td>
</tr>
<tr>
<td>Polyoxyethylated glycerides (Labrafil M 2125 Cs)</td>
<td>Sandimmune soft gelatin capsules</td>
</tr>
<tr>
<td>Polyoxyethylated oleic glycerides (Labrafil M1944 Cs)</td>
<td>Agenerase Soft gelatin capsule, Agenarage oral solution</td>
</tr>
<tr>
<td>D-alpha Tocopheryl polyethylene glycol 1000 succinate (TPGS)</td>
<td>Neoral soft gelatin Capsule, Nerol Oral Solution, Gengraf hard gelatin Capsule, Sandimmune soft gelatin Capsule,</td>
</tr>
<tr>
<td><strong>Co-solvents</strong></td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td>Sandimmune oral solution</td>
</tr>
<tr>
<td>Glycerin</td>
<td>Neoral soft gelatin Capsule, Sandimmune soft gelatin Capsules</td>
</tr>
<tr>
<td>Polypylene glycol</td>
<td>Neoral soft gelatin Capsule, Nerol Oral Solution, Lamprene soft gelatin capsule, Agenarage Oral solution Gengraf hard gelatin capsule</td>
</tr>
<tr>
<td>Polyethylene glycol</td>
<td>Targretin soft gelatin capsule, Gengraf hard gelatin capsule, Agenarase soft</td>
</tr>
</tbody>
</table>
### Excipient Name (commercial name) | Examples of commercial products in which it has been used
---|---
Lipid ingredients | capsule, Agenerase oral solution
Corn oil mono, di, tri-glycerides | Neoral soft gelatin Capsule, Nerol Oral Solution
DL-alpha-Tocopherol | Neoral Oral Solution, Fortavase soft gelatin capsule
Fractionated triglyceride of coconut oil (medium-chain triglyceride) | Rocaltrol soft gelatin capsule, Hectrol soft gelatin capsule
Fractionated triglyceride of palm seed oil (medium-chain triglyceride) | Rocatrol oral solution
Mixture of mono-and di-glycerides of caprylic/capric acid | Avodat soft gelatin capsule
Medium chain mono-and di-glycerides | Fortavase soft gelatin capsule
Corn oil | Sandimmune soft gelatin capsule, Depakene capsule
Olive oil | Sandimmune oral solution
Oleic acid | Ritonavir soft gelatin capsule, Norvir soft gelatin capsule
Sesame oil | Marinol soft gelatin capsule
Hydrogenated soyabean oil | Accutane soft gelatin capsule, Vesanoid soft gelatin capsule
Hydrogenated vegetable oils | Accutane soft gelatin capsule, Vesanoid soft gelatin capsule
Soyabean oil | Accutane soft gelatin capsule
Peanut oil | Vesanoid soft gelatin capsule
Beeswax | Vesanoid soft gelatin capsule

**1.5 Formulation of SEDDS**

SEDDS are composed of oil, hydrophilic surfactant, and a co-solvent. The process of self-emulsification is only specific to certain combinations of pharmaceutical excipients. It depends on the type of oil and surfactant pair, their ratios, the surfactant concentration and the temperature at which self-emulsification occurs. The primary step...
during formulation of a SEDDS is the identification of these specific combinations of excipients and construct a phase diagram which shows various concentrations of excipients that possess self-emulsification. Mutual miscibility of these excipients is also important for producing a stable liquid formulation. Long chain triglycerides (LCT) are usually immiscible with hydrophilic surfactants and co-solvents. Polar oils such as mixed glycerides show an affinity towards hydrophilic surfactants and thus are miscible with the surfactant and also aids in self-dispersion of the formulation. The diversity of the chemical nature of lipids used may lead to immiscibility on long-term storage, so it is essential to perform physical stability tests on the formulation. If waxy excipients are used, they should be melted before weighing and then mixed with other liquid excipients (Pouton & Porter 2008). With a large variety of liquid or waxy excipients available, ranging from oils through biological lipids, hydrophobic and hydrophilic surfactants, to water soluble co-solvents, there are many different combinations that could be formulated for encapsulated in hard or soft gelatin or mixtures which disperse to give fine colloidal emulsions. The following should be considered in the formulation of a SEDDS:

1. The solubility of the drug in different oil, surfactants and co-solvents.
2. The selection of oil, surfactant and co-solvent based on the solubility of the drug and the preparation of the phase diagram (Farah & Laforet, 1994).
3. The preparation of SEDDS formulations by dissolving the drug in a mixture of oil, surfactant and co-solvent. The addition of a drug to a SEDDS is critical because the drug interferes with the self emulsification process to a certain extent, which leads to a change in the optimal oil–surfactant ratio. So, the design of an optimal SEDDS requires preformulation solubility and phase-diagram studies. In the case of prolonged SEDDS, formulation is made by adding the polymer or gelling agent (Nazzel & Khan, 2006).

1.6 Excipients used in SEDDS

**Tween 80**

Tween 80 is the partial fatty acid ester of sorbitol and it forms anhydrides as a result of copolymerization of approximately 20 moles of ethylene oxide for each mole of sorbitol. They are hydrophilic nonionic surfactants (HLB-15) and are used as
emulsifiers in the preparation of oil-in-water emulsions, oral and injectable suspensions and solutions and as solubilizing agents for oil soluble vitamins (Nielloud, 2000).

Tween 80 has been reported to protect proteins from surface induced denaturation during freeze drying (Chang & Kendrick, 1996). It is one of the most widely used surfactant in the preparation of self dispersing type of formulations (Gershaink & Benita, 2000). It is approved by the FDA for oral use. Peroxide impurities present in Tween 80 cause protein denaturation when such products are stored for extended periods of time.

Cremophor RH 40

It is a polyoxyethylene of derivative castor oil containing 70% of components which are hydrophobic in nature with an HLB of 14-16. Cremophor RH 40 contains fatty acid esters of glycerol polyethylene glycol and fatty acid esters of polyethylene glycol. It aids in improving aqueous solubility of propellant in water based aerosol vehicles. It is used as a solubilizing agent for various hydrophobic active pharmaceutical ingredients (API), fat soluble vitamins, and essential oils; and as an emulsifier in the preparation of pharmaceutical emulsions and SEDDS. It aids in solubilization of Lopinavir and Ritonavir in Kaletra® oral solution and Cyclosporine in Neoral® oral microemulsions (Strickley R et al. 2000).

Labrafac Lipophile WL 1349

Labrafac Lipophile WL 1349 is a medium chain triglyceride of fractionated vegetable C8 and C10 fatty acids (mainly fractionated coconut oil or palm kernel oil) with an HLB of 1. It is a non rancidable fluid used as a vehicle in oral and topical preparations, emulsions, self-emulsifying drug delivery systems, suspensions, ointments, suppositories, and creams. It can be used as filler in capsules and as an antiadherent in tablets. In combination with long chain triglycerides, it serves as a total parenteral nutrition (TPN) component. They possess excellent spreadability, skin penetration, and solvent properties when compared to long-chain triglycerides (Knepp V et al. 1996).

Polyethylene Glycol 400

Polyethylene glycols (PEG) have a wide range of applications including topical, oral, parenteral, ophthalmic and rectal delivery. Liquid grade PEG”s are used as a water
miscible co-solvents which possess good solvent properties for poorly water soluble drugs. Due to this property, they are widely used in lipid based drug delivery systems such as solid dispersions and self-emulsifying mixtures. When used in soft gelatin capsules, they are known to cause hardening of capsule shells by absorption of moisture from the gelatin in the shell.

**Capyrol 90**

Soluble in ethanol, chloroform, methylene chloride, and vegetable oils, insoluble in water Capryol 90 contains more than 90% monoester of C8 fatty acid (caprylic acid). It is used as an emulsifier in oil-in-water emulsions and self emulsifying drug delivery systems. It is reported to possess bioavailability enhancing properties due to its inhibitory action on CYP3A4 enzyme (Kakute et al. 2008).

**Transcutol P**

Transcutol P has good solvent properties of poorly water soluble drugs. It enhances drug penetration, permeation, and produces a drug depot effect. It is used as a co-solvent in the formulation of SMEDDS (Stuhlneier et al. 1999).

**Neusilin US2**

Neusilin US2 is a very fine powder of amorphous magnesium aluminosilicate. It possesses a very large surface area enabling it to adsorb oils up to three times of its weight. It has good flowability and compressibility and can be directly compressed into tablets. It has been used as an adsorbent for oil-emulsifier mixtures (Ito et al. 2005), in SEDDS and for melt granulation in solid dispersion technology. Upon co-grinding with a crystalline drug, it converts the drug into an amorphous form (Gupta et al. 2003).

**1.7 DOSAGE FORM OF SEDDS:**

**1.7.1 Oral Delivery**

**(a) Self emulsifying capsule (Morozowich et al. 2009)**

After administration of capsules containing conventional liquids SE formulations, microemulsion droplets form and subsequently disperse in the GIT to reach the site of absorption. If irreversible phase separation of microemulsion occurs an improvement of drug absorption can’t be expected. For handling this problem, sodium dodecyl sulfate was added into the SE formulation.
(b) Self-Emulsifying sustained / controlled release tablets: (Lip et al. 2005)
Combination of lipids and surfactant has presented great potential preparing SE tablets. SE tablets are of great utility in obviating adverse effect. Inclusion of indomethacin (or other hydrophobic NSAID) for example, into SE tablets may increase its penetration efficacy through the GI mucosal membrane, potentially reducing GI bleeding.

(c) Self emulsifying sustained / controlled release pellets: (Lip et al. 2005)
Pellets, as a multiple unit dosage form, possess many advantages over conventional solid dosage form, such as flexibility of manufacture, reducing intra subject and inter subject variability of plasma profile and minimizing GI irritation without lowering drug bioavailability.

(d) Self emulsifying solid dispersions: (Itoh et al. 2002)
Solid dispersions could increase the dissolution rate and bioavailability of poorly water soluble drugs, but still some manufacturing difficulties and stability problems existed. Serajuddin pointed out that these difficulties could be surmounted by the use of excipients.

1.7.2 Topical Delivery
Topical administration of drugs can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first pass metabolism of the drugs and related toxic effects.

1.7.3 Ocular and Pulmonary delivery
For the treatment of eye disease, drugs are essentially delivered topically o/w microemulsion have been investigated for ocular administration, to dissolve poorly soluble drugs, to increase absorption and to attain prolong release profile.

1.7.4 Parenteral delivery
Parenteral administration of drugs with limited solubility is a major problem in the industry because of the extremely low amount of the drug actually delivered as target site.

1.8 BIOPHARMACEUTICAL ASPECTS
The ability of lipids and/or food to enhance the bioavailability of poorly water soluble drugs is well known. Although incompletely understood, the currently accepted view is
that lipids may enhance bioavailability via a number of potential mechanisms, including.

a) Alterations (reduction) in gastric transit.
b) Increases in effective luminal drug solubility.
c) Stimulation of intestinal lymphatic transport.
d) Changes in the biochemical barrier function.
e) Changes in the physical barrier function of the GI tract.
f) The polarity of lipid phase is one of the factors that govern the release from the micro-emulsion.

1.9 Solid SEDDS

SEDDS can exist in either liquid or solid states. SEDDS are usually, however, limited to liquid dosage forms, because many excipients used in SEDDS are not solids at room temperature. Given the advantages of solid dosage forms, solid self-micro emulsifying drug delivery system, S-SEDDS have been extensively exploited in recent years, as they frequently represent more effective alternatives to conventional liquid SEDDS.

From the perspective of dosage forms, S-SEDDS mean solid dosage forms with self-emulsification properties. S-SEDDS focus on the incorporation of liquid/semisolid SE ingredients into powders/nanoparticles by different solidification techniques. To some extent, S-SEDDS are combinations of SEDDS and solid dosage forms, so many properties of S-SEDDS (e.g. excipients selection, specificity, and characterization) are the sum of the corresponding properties of both SEDDS and solid dosage forms. For instance, the characterizations of SE pellets contain not only the assessment of self-emulsification, but also friability, surface roughness, and so on. In the 1990s, S-SEDDS were usually in the form of SE capsules, SE solid dispersions and dry emulsions, but other solid SE dosage forms have emerged in recent years, such as SE pellets/tablets, SE micro-spheres/nanoparticles and SE suppositories/implants (Ajay Kumar et al. 2010).

Thus, S-SEDDS combine the advantages of SEDDS (i.e. enhanced solubility and bioavailability) with those of solid dosage forms (e.g. low production cost, convenience of process control, high stability and reproducibility, better patient compliance.). (Ruchita Patel et al. 2013)
1.9.1 METHOD OF PREPARATION: (Gao P et al. 2008)

Solidification techniques for transforming liquid/semisolid: Various solidification techniques are as listed below;

A) Capsule filling with liquid and semisolid self-emulsifying formulations:
Capsule filling is the simplest and the most common technology for the encapsulation of liquid or semisolid SE formulations for the oral route.
For semisolid formulations, it is a four-step process:
   a) Heating of the semisolid excipient to at least 20°C above its melting point.
   b) Incorporation of the active substances (with stirring).
   c) Capsule filling with the melt cooling to room temperature. For liquid formulations, it involves a two-step process.
   d) Filling of the formulation into the capsules followed by sealing of the body and the cap of the capsule, either by banding or by micro spray sealing.

B) Spray drying
Essentially, this technique involves the preparation of a formulation by mixing lipids, surfactants, drug, solid carriers, and solubilization of the mixture before spray drying. The solubilized liquid formulation is then atomized into a spray of droplets.

The droplets are introduced into a drying chamber, where the volatile phase (e.g. the water contained in an emulsion) evaporates into the chamber and the drying chamber design are selected according to the drying characteristic the product and powder specification.

C) Adsorption to solid carriers
Free flowing powders may be obtained from liquid SE formulations by adsorption to solid carriers. The adsorption process is simple and just involves addition of the liquid on to carriers by mixing in a blender.

D) Melt granulation
Melt granulation is a process in which powder agglomeration is obtained through the addition of a binder that melts or softens at relatively low temperatures.
E) Melt extrusion/extrusion spheronization

Melt extrusion is a solvent-free process that allows high drug loading (60%), as well as content uniformity. Extrusion is a procedure of product of uniform shape and density, by forcing it through a die under controlled temperature, product flow, and pressure conditions.

1.10 Nanoemulsion Gel

The U.S.P defines gels as a semisolid system consisting of dispersion made up of either small inorganic particle or large organic molecule enclosing and interpenetrated by liquid. Gel is a semisolid system of at least two interpenetrating phases: a gelling agent and a liquid. When gel and nanoemulsion are used in combination, the dosage forms are referred as nanoemulsion gel. Nanoemulsion gels have emerged as one of the most interesting topical delivery system as it has dual release control system i.e. gel and emulsion. The major objective behind this formulation is the delivery of hydrophobic drugs to the systemic circulation via the skin. Nanotechnology with the use of nano sized particles has largely succeeded in overcoming skin barriers and hence nano sized emulsion easily penetrate the pores of the skin and reach the systemic circulation thus getting channelized for effective delivery. (Nemade P.S etal. 2014)

1.10.1 Advantages of using nanoemulsion gel as Topical Drug Delivery System

(Patel Rahul etal. 2014)

Hydrophobic drugs can be easily incorporated by using (o/w) nanoemulsion in to gels. Most of the hydrophobic drugs cannot be incorporated directly into the gel base because solubility act as a barrier and a problem arises during the release of the drug. Nanoemulsion gel helps in the incorporation of hydrophobic drugs into the oil phase and then oily globules are dispersed in an aqueous phase resulting in (o/w) nanoemulsion and this nanoemulsion can be mixed into gel base. This may provide better stability and release of drug than simply incorporating drugs into gel base.

Better Stability

Nanoemulsion based gel preparations are more stable than other topical preparations. Like dusting powders which are hygroscopic, creams shows phase inversion or creaming and ointment shows rancidity due to oily base.
Production feasibility and low production cost
Preparation of nanoemulsion based gels comprises of simpler and short steps which increases the feasibility of the production. There are no specialized instruments needed for the production of microemulsion based gels. Moreover, materials used are easily available and cheaper. Hence, decrease the production cost of microemulsion based gels.

No intensive sonication
Production of vesicular molecules needs intensive sonication which may result in drug degradation and leakage. As no sonication is needed, this problem is not seen during the production of nanoemulsion based gels

Controlled release
Nanoemulsion based gels can be used to prolong the effect of drugs having a shorter half life.

1.10.2 Classification of gelling agent
The addition of gelling agent to nanoemulsion formulations gives a gelled structure. Gelling agent are of two types: natural and synthetic. Incorporation of gelling agents in a system makes it thixotropic. Gelling agents are hydrophilic in nature, its cross-linked structure and their insolubility in water makes them a potential candidate for use in controlled release drug delivery system. Effect of gelling agent has been studied on the release rate of drug from nanoemulsion based gel. It has been found that is an inverse correlation between the concentration of gelling agent and the extent of drug released. Others type, including synthetic, semi-synthetic, natural gelling agent can also be employed.

Gels are classified mainly by two methods based on:

a) Nature of colloid phase
   i) Inorganic gels
   ii) Organic gels

b) Based on the nature of the solvent
   i) Aqueous gels
   ii) Non aqueous gels
1.10.3 Gel forming substances:
Polymers are used to give the structural network, which is essential for the preparation of gels. Gel forming polymers are classified as follows:

Table 1.8: Classification of gel forming agents: (Nemade P S 2014)

<table>
<thead>
<tr>
<th>S.No</th>
<th>Types</th>
<th>Subtypes</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Natural polymer</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Proteins</td>
<td>Collagen, Gelatin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polysaccharides</td>
<td>Agar, Alginate acid, Sodium or Potassium carageenan, Tragacanth, Pectin, Guar Gum, Cassia tora, Xanthan, Guar Gum</td>
</tr>
<tr>
<td>2</td>
<td>Semisynthetic polymers</td>
<td>Cellulose derivative</td>
<td>Carboxy-methyl-cellulose, Methyl-cellulose, Hydroxy-propyl cellulose, Hydroxy-propyl-methyl-cellulose, Hydroxyethyl cellulose.</td>
</tr>
<tr>
<td>3</td>
<td>Synthetic polymers</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carbomer</td>
<td>Carbopol 940, Carbopol 971, Carbopol 934, Carbopol 974</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surfactants</td>
<td>Cetostearyl alcohol, Brij-96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Others</td>
<td>Polyacrylamide, Polyethylene and its co-polymer, Aluminium hydroxide</td>
</tr>
</tbody>
</table>

Table 1.9 Various gelling agent used for formulation of Nanoemulsion gel:

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Gelling agent</th>
<th>Advantages</th>
<th>Concentration (%w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Carbopol-934</td>
<td>Form gels at very low concentration and provide control release of incorporated drug</td>
<td>1%, 1.78%</td>
</tr>
<tr>
<td>2</td>
<td>Carbopol-940</td>
<td>Form highly viscous gels and provides controlled release of incorporated drug</td>
<td>1%</td>
</tr>
<tr>
<td>3</td>
<td>HPMC-2910</td>
<td>Produce neutral gels of very stable viscosity</td>
<td>2.5%, 5%</td>
</tr>
<tr>
<td>4</td>
<td>Sodium CMC</td>
<td>Suitable for sterile gels as it can stand autoclaving without serious deterioration</td>
<td>3-4%</td>
</tr>
</tbody>
</table>
1.11 Evaluation of Nanoemulsion Gel

Physical appearance
The prepared nanoemulsion gels were inspected for their color, homogeneity, consistency and pH. The pH values of 1% aqueous solutions of the prepared gellified nanoemulsion are measured by a pH meter.

Spreadability measurement
To determine the spreadability of nanoemulsion based gel, 0.5 g of gel was placed within a circle of 1 cm diameter pre-marked with a glass plate, over which a second glass plate was placed. A weight of 500g was allowed to rest on the upper glass plate for 5min. The increase in the diameter due to gel spreading was noted.

Rheological study
The viscosity of nanoemulsion based gel formulation was determined at 37°C using a brookfield viscometer, spindle no S-64, at varying rpm (0.5 to 100 rpm).

Drug content determination
1gm of nanoemulsion based gel was taken and mixed in a suitable solvent. The solution was filtered and absorbance was determined using UV spectrophotometer. Standard plot of drug is prepared in the same solvent. Concentration and drug content can be determined by using the same standard plot by putting the value of absorbance.

Extrudability (Tube test)
It is a usual empirical test to measure the force required to extrude the material from the tube. The method adopted for evaluating nanoemulsion gel for extrudability is the weight in grams required to extrude at least 0.5 cm ribbon of nanoemulsion gel in 10 seconds from aluminium collapsible tube. More quantity extruded better is extrudability. The extrudability is calculated by using the following formula:

\[
Extrudability = \frac{\text{Applied weight to extrude nanoemulsion gel from tube (g)}}{\text{Area (cm. cm)}}
\]
**In vitro release study/ permeation studies**

Franz diffusion cell was used for the drug release studies. Nanoemulsion gel was applied onto the surface of dialysis membrane evenly. The dialysis membrane was clamped between the donor and the receptor chamber of diffusion cell. The receptor chamber was filled with freshly prepared PBS (pH 6.8) solution. The samples were collected at a suitable time interval and replaced with fresh medium in order to maintain sink conditions. Samples were analyzed for drug content by a UV spectrophotometer at a suitable wavelength after appropriate dilutions. The cumulative amount of drug released was determined as a function of time.

**1.12 Absorption of SEDDS (Lathika M et al. 2013)**

Generally the SEDDS causes the stimulation of intestinal lymphatic transport. For highly lipophilic drugs, lipids may enhance the extent of lymphatic transport and increase bioavailability directly or indirectly via a reduction in first pass metabolism. Increases in effective luminal drug solubility. The presence of lipids in the GI tract stimulates an increase in the secretion of bile salts (BS) and endogenous biliary lipids including phospholipids (PL) and cholesterol (CH), leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilisation capacity of the GI tract. However, the intercalation of administered (exogenous) lipids into these BS structures either directly (if sufficiently polar), or secondary to digestion, leads to swelling of the micelle structures and a further increase in solubilisation capacity. Changes in the biochemical barrier function of the GI tract. It is clear that certain lipids and surfactants may attenuate the activity of intestinal efflux transporters, as indicated by the p-glycoprotein efflux pump, and may also reduce the extent of enterocyte-based metabolism. - Rapid dispersion of self-emulsifying systems - Increased solubility and promotion of super saturation - Increasing residence time - Potential effects on intestinal-based efflux and permeability - Potential influence of drug metabolism in the intestine.
1.13 Evaluation of SEDDS: (Patil & Vandana 2007)

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 physical stability can lead to phase separation of the excipient, affecting not only formulation performance, but visual appearance as well. In addition, incompatibilities between the formulation and the gelatin capsule shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of the drug.

1. **Heating cooling cycle**: Six cycles between refrigerator temperature (40°C) and 45°C with storage at each temperature of not less than 48hrs is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.

2. **Centrifugation**: Formulations were centrifuged at 3500rpm for 30 min, and examined for phase separation.

3. **Freeze thaw cycle**: The formulations were subjected to freeze thaw cycles between -4°C and 40°C for not less than 48hrs at each temperature. Those
formulations that passed this test showed good stability with no phase separation, creaming, or cracking.

Dispersibility test
The efficiency of self-emulsification of oral nano or micro emulsion is assessed using a standard USP XXII dissolution apparatus 2. One milliliter of each formulation was added to 500 ml of water at 37±0.5°C

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 formed 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 SEDDS formulation.

Turbidimetric Evaluation
Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of Selfemulsifying 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 is not possible to monitor the rate of change of turbidity (rate of emulsification).
Viscosity Determination
The SEDDS system is generally administered in soft gelatin or hard gelatin capsules. So, it can be easily pourable into capsules and such system should not too thick to create a problem. The rheological properties of the micro emulsion are evaluated by Brookfield Viscometer. This viscosities determination conforms whether the system is w/o or o/w. If system has low viscosity then it is o/w type of the system and if high viscosities then it is w/o type of the system.

Droplet Size Analysis, Particle Size Measurements
The droplet size of the emulsions is determined by photon correlation spectroscopy (which analyses the fluctuations in light scattering due to Brownian motion of the particles) using a Zetasizer 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. The nanometric size range of the particle is retained even after 100 times dilution with water, which proves the system’s compatibility with excess water.

Zeta Potential
The surface charge is measured using a zeta sizer at 25°C by measuring zeta potential of the prepared formulation. After suitable dilution with distilled water the zeta potential is measured. The values are determined from the electrophoretic mobility of the oil droplets. The charge of the oil droplets in conventional SEDDS is negative due to the presence of free fatty acids, however incorporation of cationic lipid, such as oleylamine will yield cationic lipids.

Refractive Index and Percent Transmittance
Refractive index and percent tranmittance proved the transparency of formulation. The refractive index of the system is measured by refractometer by placing drops of solution on the slide and it compare with water (1.333). The percent transmittance of the system is measured at a particular wavelength using UV-spectrophotometer keeping distilled water as blank. If refractive index of system is similar to the refractive index of water
(1.333) and formulation have percent transmittance > 99 percent, then formulation has transparent nature.

**Electro conductivity Study**

The SEDD system contains ionic or non-ionic surfactant, oil, and water. So, this test is used to measure the nature of systems. The electro conductivity of resultant system is measured by electroconductometer.

**In Vitro Diffusion Study**

In vitro diffusion studies is performed to study the release behavior of formulation from liquid crystalline phase around the droplet using the dialysis technique.

**Drug content**

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

**Evaluation Of Solid SEDDS**

In addition to the above mentioned evaluation parameters, outer macroscopic structure of solid SEDDS can be investigated by scanning electron microscope. Physical state of drug in solid SEDDS must be investigated as it may affect drug release as well bioavailability of drug. Drug must be present in dissolved state throughout product’s self-life. Differential Scanning Calorimetric method as well X-Ray diffraction can be used for this purpose.

**In vitro Drug Release from Solid SEDDS:**

Every solid dosage forms must be evaluated for release of drug form that dosage form. Usually in vitro dissolution is used for determination of drug release form solid selfemulsifying formulation. USP-II type dissolution apparatus containing appropriate dissolution media should be used for conducting drug release study.
1.14 Applications of SEDDS (Patel P.A 2008)

**Improvement in Solubility and bioavailability:** If the drug is incorporated in SEDDS, it increases the solubility because it circumvents the dissolution step in case of Class-II drug (Low solubility/high permeability). Ketoprofen, a moderately hydrophobic (log P 0.979) nonsteroidal anti-inflammatory drug (NSAID), is a drug of choice for sustained release formulation has high potential for gastric irritation during chronic therapy. Also, because of its low solubility, ketoprofen shows incomplete release from sustained release formulations. Vergote et al. (2001) reported complete drug release from sustained release formulations containing ketoprofen in nanocrystalline form.70 Different formulation approaches that have been sought to achieve sustained release, increase the bioavailability, and decrease the gastric irritation of ketoprofen include preparation of matrix pellets of nano-crystalline ketoprofen,70 sustained release ketoprofen microparticles71 and formulations71, floating oral ketoprofen systems72, and transdermal systems of ketoprofen. 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, an increase in AUC i.e. bioavailability and Cmax is observed with many drugs when presented in SEDDS.

**Protection against Biodegradation**

The ability of self emulsifying drug delivery system to 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. Many drugs are degraded in physiological system, because of acidic pH in stomach, enzymatic degradation or hydrolytic degradation etc. Such drugs when presented in the form of SEDDS can be well protected against these degradation processes as liquid crystalline phase in SEDDS might be an act as barrier between degradating environment and the drug. Acetylsalicylic acid (Log P = 1.2, Mw=180), a drug that degrades in the GI tract because it is readily hydrolyzed to salicylic acid in an acid environment. When the drug was formulated in a Galacticles™ Oral Lipid Matrix System (SEDDS formulation) and compared to a commercial formulation, it showed the good plasma profile. The oral bioavailability of undegraded acetylsalicylic acid is improved by 73% by the
Galacticles™ Oral Lipid Matrix System formulation compared to the reference formulation. This suggests that the SEDDS formulation has a capacity to protect drugs from degradation in the GI tract. low oral bioavailability.