SMEDDS/SNEDDS: AN EMERGING TECHNIQUE TO SOLUBILITY ENHANCEMENT FOR THE PHARMACEUTICAL INDUSTRY

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ABSTRACT

Most of the new chemical entity (NCE) used today have poor bioavailability due to numerous formulation related performance issues and to ensure the compliance of oral drugs for their long term use have become a prerequisites. Lipid based formulation is one of the growing and suitable drug delivery strategies to overcome the issue of bioavailability and dissolution rate of Poorly water soluble drugs (especially BCS Class II and IV) for better dispersion. Thus, it is stated that over 30% of the drug candidate’s entities are hydrophobic in nature or lacking required aqueous solubility. SMEDD/SNEDDS are isotropic mixture of oil, surfactant and co-surfactant molecules used in the formulations to improve the oral absorption of highly lipophilic drugs. These systems have unique property to form oil in water emulsion under gentle agitation provided by digestive motility of the stomach and intestine. The aim of the current review is to screen lipid excipients for their self-emulsification efficiency and to overcome the limitation of liquid SMEDDS/SNEDDS in handling, stability problem, precipitation of drug delivery fabrication and unsuitable for hydrophobic drugs. The review also aims to conversion of liquid SMEDDS/SNEDDS to S-SMEDDS/S-NEDDS to enhance the oral bioavailability of poorly soluble and low absorption drugs of various solid dosage forms by using adsorption on solid carrier, spray drying, lyophilization, and melt granulation and extrusion techniques.

KEYWORDS: Poorly water soluble drugs, Solid- self micro and nano emulsifying delivery, Lipid based formulation, Techniques, Bioavailability and absorption.

INTRODUCTION

Drive innovation and lead change: Continuous innovation is one of the pharmaceutical industry’s most defining characteristics. During innovation includes intensive research
coverage, giving rise to abundant but relatively dispersed knowledge of the mechanisms, driving drug discovery and development. Research on the forefront of science, the creation of new knowledge bases, the invention of new medicines and the improvement of existing drugs constitute the fuel that propels the pharma industry.

For successful development of pharmaceutical formulation, new chemical entity is one of the key points for the adequate aqueous solubility. Along with the emergence of drug design, various molecules have been created that have a prospective for therapeutic action. But due to this, most of the newly discovered drug candidate and many drug existing drug molecules are of high molecular weight, high intra and inter- subject variability, and lack of dose proportionality and hence it limits the bioavailability of orally administered drugs.[1] Therefore, due to above characteristics, it limits the bioavailability of orally administered drugs. Hence, due to have low solubility of drugs, this leads to low dissolution and therefore limits the absorption.[2] To overcome this dilemma, some clinical formulations have been developed, but low oral bioavailability of most drugs is still a major obstacle leading to challenges for pharmaceutical manufacturers to design delivery systems that can be improved by increasing its gastrointestinal solubilization with modification of pharmacokinetic action and therapeutic responses.[3]

**ROUTES OF DRUG ADMINISTRATION**

The route for drug administration refers to the way through which the drug gets inside the body and gets absorbed into the bloodstream. The various routes for dosage administration are oral, parenteral, topical and mucous membrane. The route of administration depends on the class of drug, associated dosage form and over the drug target or medication. In most administration routes, either oral, transmucosal or parenteral, only a fraction of the administered drug is effectively delivered to its intended target. In oral administration the endothelial cell or enterocytes of the intestine is selectively permeable but the drug is exposed to varying range of conditions that may cause its degradation or inactivation. Oral drug delivery system is the appropriate and most favored route for drug administration as it has better therapeutic effects, more economy, non-invasive, good patient compliance i.e., painlessly administered resulting in high acceptability especially easy method for chronic disease, protect the drug from the degradation in the gastrointestinal tract and deliver the bioactive compounds to the specific area where it is better absorbed. Due to this, substantial effort had been made in the betterment of oral drug delivery, drug stability in the GIT,
increasing drug solubility and bioavailability, toxicity and disposition within the body in order to obtain the desired drugs in a safe and efficacious form.[2]

BIOPHARMACEUTICAL CLASSIFICATION SYSTEM

Any formulation of drugs is carried out with the motive of enhancing the bioavailability. Poor water soluble drugs are challenging for the researchers with regard to solubility and bioavailability. Aqueous solubility, gastrointestinal drug permeability, dissolution rate and first pass metabolism are parameters that control the rate and extent of drug absorption and its bioavailability. The water solubility of a drug is a fundamental property that hampers the absorption of drug after oral administration and also the backbone for oral bioavailability of drug. Biopharmaceutical classification system is a scientific classification of a drug substance depends on its aqueous solubility and intestinal permeability that correlated in-vitro dissolution and in-vivo bioavailability of drug products.[4] BCS is very useful device for decision making in the discovery and early development of new and existing drugs. BCS direction was provided by USFDA to improve the efficiency of drug product development process. It is a system which is mainly used to differentiate the drugs on the basis of their solubility and permeability. It also allows for the prediction of in vivo pharmacokinetics of oral immediate-release (IR) drug products by classifying drug compounds into four classes based on their solubility related to dose and intestinal permeability with the dissolution properties of the dissolution form.[5] Three parameters on which BCS classification depends upon: Solubility, intestinal permeability and dissolution rate, all of them governs the rate and extent of oral drug absorption from IR solid oral dosage forms.[6]

Table 1: BCS CLASSIFICATION SYSTEM[7]

<table>
<thead>
<tr>
<th>BCS Classification</th>
<th>Solubility</th>
<th>Permeability</th>
<th>Examples</th>
<th>Hurdles minimize by SMEDDS/SNEDDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>High</td>
<td>High</td>
<td>Diltiazem, Metoprolol</td>
<td>Dissolution, nor absorption, rate limiting</td>
</tr>
<tr>
<td>Class II</td>
<td>Low</td>
<td>High</td>
<td>Phenytoin, Mebendazole</td>
<td>Dissolution/solubilisation “rate determining”</td>
</tr>
<tr>
<td>Class III</td>
<td>High</td>
<td>Low</td>
<td>Acyclovir, Neomycin</td>
<td>Poor predictability, other mechanisms in vivo</td>
</tr>
<tr>
<td>Class IV</td>
<td>Low</td>
<td>Low</td>
<td>Furosemide, Taxol</td>
<td>Novel alternative approaches to bypass body function</td>
</tr>
</tbody>
</table>

Lipid Based Drug Delivery System (LBDDS)

In modern molecular pharmaceutics, advanced delivery technologies such as lipid-based drug delivery system (LBDDS) plays a crucial role in formulating hydrophobic drugs (poor water
soluble) by using lipids as carriers. In lipid-based systems, the poorly soluble drug is completely utilized in lipid molecules alone or in combination with other biocompatible materials, to present a drug in a more compatible form to the biological system. Therefore, for poorly soluble drugs, when the drug exists in lipid formulation at molecular level it gives great probability for better absorption.\textsuperscript{[8]} Additionally, to improving solubility and bioavailability, lipid drug delivery also provide many other clinical advantages over conventional formulations for poorly soluble compounds such as: Lowering of therapeutic dose due to improved drug absorption, Reduction or elimination of intra- and inter- subject variability due to reduced effects of gastrointestinal variability on solubilization, Reduction or elimination of food effects on bioavailability of a compound thus improving dosing flexibility, Reduction in hepatic metabolism due to potential transport of compounds through lymphatic system and Improved dose uniformity. Factors which should be concede in designing of lipid- based formulation are properties of lipid excipients (the hydrophobic sink), lipophilicity of the surfactant (to aid emulsification /solubilisation, excipient digestion in GIT and solvent miscibility (to aid salvation /dispersion).\textsuperscript{[8]}

**TABLE: 2 CLASSIFICATION OF LIPID BASED FORMULATION\textsuperscript{[9]}**

<table>
<thead>
<tr>
<th>Formulation Type</th>
<th>Materials</th>
<th>Characteristics</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Oils without surfactants (tri-di &amp; monoglycerides)</td>
<td>Non-dispensing require digestion</td>
<td>Generally recognize as a safe status, simple excellent capsule compatibility</td>
<td>Formulation has poor solvent capacity unless drug is highly lipophilic</td>
</tr>
<tr>
<td>Type II</td>
<td>Oils and water insoluble surfactants</td>
<td>SEDDS formed without water soluble components</td>
<td>Unlikely to lose solvents capacity on dispersion</td>
<td>Turbid o/w dispersion</td>
</tr>
<tr>
<td>Type III</td>
<td>Oil, surfactants co-solvents (Both water Soluble and insoluble Excipients)</td>
<td>SEDDS/SMEDDS formed with water soluble components</td>
<td>Clear or almost clear dispersion, drug absorption without digestion</td>
<td>Possible loss of solvent capacity on dispersion, less easily digested</td>
</tr>
<tr>
<td>SType IV</td>
<td>Water soluble Surfactants and co-solvents</td>
<td>Formulation disperses typically to form a micellar solution</td>
<td>Formulation has good solvent capacity for many drugs</td>
<td>Likely loss of solvent capacity on dispersion</td>
</tr>
</tbody>
</table>

**MODIFICATIONS OF LIPID-BASED DELIVERY SYSTEMS FOR DRUG DELIVERY**

To influence absorption and bioavailability, various lipid-based formulation are oily solution, oil suspension, emulsions(coarse and micro), solid-lipid particles and depending on
formulation composition, they are classified as SEDDS, SNEDDS and SMEDDS and hence self- micro or self-nano emulsifying delivery system (SMEDDS/SNEDDS) are more emphasis. These formulations provide greater bioavailability due to increased solubilization of a compound and increased surface area which results in emulsification and micro-emulsification of the lipid formulation in the GI tract. These SNEDDS/SMEDDS have been endeavor which shows that lipid vehicles are of great importance in the design and the success of drug delivery by controlling the drugs absorption rate based on their digestibility.

SELF- EMULSIFYING DRUG DELIVERY SYSTEM

Booming formulation of SNEDDS and SMEDDS depends on the complete understanding of the spontaneous emulsification process and also on the physicochemical and biological properties of the components used for the shaping of SNEDDS and SMEDDS. The factors which influence the concept of self-emulsification are: Physicochemical nature and concentration of oily phase, surfactant and co- surfactant, Ratio of the components, i.e. oil-surfactant and Smix (surfactant:co-surfactant) ratio and Temperature of the aqueous phase where nano and micro-emulsification would form.

Advantages of Self- emulsification
1. Enhanced oral bioavailability which enables reduction in dose.
2. Protection of sensitive drug substances.
3. It can be easily stored as it belongs to a thermodynamics stable system.
4. Selective targeting of drugs toward specific absorption window in GIT.
5. Fine oil droplets would pass rapidly and promote wide distribution of the drug throughout the GIT, therefore minimize the irritation frequently encountered during extended contact between bulk drug substance and the gut wall.
6. High drug payloads
7. If compared with oily solutions, they provide a large interfacial area for partitioning of the drug between oil and water

Self microemulsifying drug delivery system (SMEDDS) are single optically isotropic and thermodynamically stable multi-component fluids composed of oil, water and surfactant (usually in conjunction with a co-surfactant) that have a unique ability of forming fine oil-in-water (o/w) micro emulsions upon mild agitation followed by dilution in aqueous media, having droplet size of less than 200nm Self-nanoemulsifying drug delivery system (SNEDDS) are novel drug delivery systems which are kinetically stable transparent
dispersions consisting of emulsified oil and water systems stabilized by an interfacial film of surfactant and co-surfactant molecules having droplet diameters ranging from 50 to 100 nm.

NOTE
[The preparation method influences emulsion properties (e.g. droplet size, stability, etc.), but the nature of the final dispersion (the constituent phases) is the same in both microemulsion and nanoemulsion whether the method of preparation uses high shear (external energy, dispersion methods)].[10]

Need of SNEDDS/SMEDDDS
1. They dramatically improve the bioavailability of lipophilic molecules and essential oils by increasing drug solubilization and surface area due to small droplet size.
2. Enhance permeation across the intestinal membrane, and facilitates transcellular and paracellular absorption with the use of surfactants like cremophor.
3. Food effects which are usually observed with lipophillic drug molecules are significantly reduced by their incorporation into SNEDDS/SMEDDDS
4. They are administered as pre-concentrates, which readily form nano and micro emulsion when dispersed in the stomach or intestinal fluid
5. Normal motility of the GIT provides energy for emulsification in contrast to SLNs, NLCs, or liposome in which case large amount of external energy is required for their formulation.[11]
DRUG TRANSPORT MECHANISM OF SMEDDS/SNEDDS

SMEDDS/SNEDDS partially avoids the additional drug dissolution step prior to absorption in the GI tract. They increase the amount of solubilized drug in the intestinal fluids resulting in good drug absorption. Apart from this, absorption of the drug may also be enhanced by using lipid based excipients in the formulation. SMEDDS/SNEDDS offer oral administration of water insoluble drugs also. Once they reach the GIT, they undergo three processes; i.e,
1. Digestive
2. Absorptive
3. Circulatory.

These three phases are depicted in Figure 2. During digestion, SMEDDS/SNEDDS form a coarse emulsion, which undergoes enzymatic hydrolysis at oil water interphase and thereby gets ready for absorption phase. After formation of mixed micelles, due to interaction of fatty acid with bile, digestion process stops. The next phase of drug absorption then starts. These colloids are taken up by passive diffusion or active transport through enterocyte membrane. Some drugs may get absorbed via lymphatic circulation through chylomicrons. In circulatory phase, drug is released from chylomicrons and the residual lipid is used in body.\[12\]

EXCIPIENTS SCREENING FOR SMEDDS/SNEDDS

In order to formulate a successful SMEDDS/SNEDDS for maximum therapeutic effect, deliberation must be given to various factors such as physiochemical properties of the active moiety and excipients, potential for drug excipient interaction, physiological factors that promote or inhibit the bioavailability and other important factors such as solubilization
capacity, miscibility, physical state of the excipients at room temperature, digestibility and compatibility with shell, chemical stability etc. should be considered during the formulation.\textsuperscript{[13]} Plenty of liquid excipients available ranges from oils through biological lipids and hydrophobic and hydrophilic surfactants to water-soluble co-surfactant/ co-solvents, there are various combinations that could form colloidal emulsions. Pharmaceutical acceptability and toxicity issues of the excipients are used which make the screening of excipients are problematic. The following points should be considered in the SEDDS excipients selection:

1. Drug solubility in different oil, surfactants and co-surfactant/ co-solvents
2. The final selection of oil, surfactant and co-surfactant/co-solvent based on solubility studies and the preparation of the ternary phase diagrams.\textsuperscript{[14]}

1. Oil/ Lipid phase

Oil in self- emulsifying system is very crucial excipient which is used to solubilize the lipophilic drug in a specific amount in order to improve both drug loading, bioavailability of the hydrophobic active moiety and facilitate self emulsification but also 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 triglyceride.\textsuperscript{[11]} The selection of oil plays an important role to determine the amount of drug that can be solubilized in the system.

2. Surfactant

Surfactants with amphiphilic character (composed of polar group (hydrophilic) and nonpolar (lipophilic) group) help the solubilisation of lipophilic drugs so preventing their precipitation in the gastrointestinal lumen and to achieve the ultra low interfacial tension at the oil water interface. The surfactant used to enhance the bioavailability by various mechanisms including: improved drug dissolution in the gastrointestinal fluids, especially in the presence of bile salts, lecithin and lipid digestion mixtures, increased intestinal epithelial permeability, increased tight junction permeability and decreased/inhibited p-glycoprotein drug efflux.\textsuperscript{[13]} Surfactant molecules mainly classified depends on the nature of the hydrophilic group within the molecule.

Non-ionic surfactants mostly preferred as it possess high HLB value preferred due to their less toxicity, possess low critical micelle concentration, and for the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous phase, providing a
good self-emulsifying performance in comparison with their ionic surfactants. Selection of surfactant primarily depends on the factors such as the efficiency and rapidity to miniemulsify the selected oil, solubilizing capacity for the drug, safety (depending on the route of administration), and type of emulsion to be formulated.

**Co-surfactant/co-solvent**

Stable interfacial tension is rarely achieved by the use of single surfactants; therefore it is necessitating adding the co-surfactant. Addition of co-surfactant leads to decrease in the bending stress of interface and allows the interfacial film sufficient flexibility to take up different curvatures required to form microemulsions/nanoemulsions. Co-surfactant of HLB value 10-14 is used with surfactants together to diminish the oil water interface, fluidize the hydrocarbon region of the interfacial film and allow the spontaneous formation of micro emulsion. The choice of co-surfactant and surfactant is critical not only to form the formation of microemulsion but also to solubilization in microemulsions.\[14\]

3. **Consistency builder**

To modify the stability of the emulsion Tragacanth, cetyl alcohol, stearic acid or beeswax can be added to formulate SMEDDS/SNEDDS.\[15\]

4. **Polymer**

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 for the formulation of sustained release SMEDDS. Examples are hydroxypropylmethyl cellulose and ethyl cellulose.\[16\]

5. **Solid carrier**

Solid carriers can be microporous inorganic substances, high surface-area colloidal inorganic adsorbent substances, cross-linked polymers, or nanoparticle adsorbents, for example, silica, silicates, magnesium trisilicate, magnesium aluminium silicate (Neusilin) microporous calcium silicate (Florite TM RE) magnesium hydroxide, talcum, crospovidone, cross-linked sodium carboxymethyl cellulose, and cross-linked polymethyl methacrylate can be adsorbed at high levels (up to 70%w/w) onto suitable carriers.\[17\]
Table 2: Various oils, surfactant and co-surfactant used in SMEDDS/SNEDDS formulation.\cite{18,19,12}

<table>
<thead>
<tr>
<th>LIPIDS</th>
<th>SURFACTANT</th>
<th>CO-SURFACTANT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oleic acid</td>
<td>Span 80</td>
<td>PEG 400</td>
</tr>
<tr>
<td>Peceol</td>
<td>Cremophore</td>
<td>Transcutol HP</td>
</tr>
<tr>
<td>Capryol 90</td>
<td>Tween 80</td>
<td>Propylene glycol</td>
</tr>
<tr>
<td>Miglyol</td>
<td>Labrasol</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Olive oil</td>
<td>Lauroglycol</td>
<td>Propylene glycol</td>
</tr>
<tr>
<td>Groundnut oil</td>
<td>Tween 85</td>
<td>dicaprylate</td>
</tr>
<tr>
<td>Maisine</td>
<td>Labrafac</td>
<td>Gelucire</td>
</tr>
<tr>
<td>Rice bran oil</td>
<td>Cremophore RH 40</td>
<td>Plurol oleique CC 497</td>
</tr>
<tr>
<td>Labrafac</td>
<td>Tween 20</td>
<td>Lutrol F127</td>
</tr>
<tr>
<td>Castor oil</td>
<td>Solutol HS 15</td>
<td>PEG 600</td>
</tr>
<tr>
<td>Capmul MCM</td>
<td>Vitamin E</td>
<td>PEG 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Akomed (caprylic and capric acid)</td>
</tr>
</tbody>
</table>

**Mechanism of self emulsification**

According to Reiss, Self-emulsification occurs when the entropy change that favours dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of the conventional emulsion is a direct function of the energy required to create a new surface between the oil and water phases and can be described by the

\[
DG = S \times N \times r \times s \quad \text{......... (Equation 1)}
\]

Where, \(DG\) = free energy associated with the process,
\(N\) = number of droplets,
\(r\) = radius of droplets,
\(s\) = interfacial energy.

The two phases of emulsion tend to separate with time to reduce the interfacial area and afterwards, the emulsion is stabilized by emulsifying agents, which form a monolayer of emulsion droplets and hence reduce the interfacial energy as well as providing an obstacle to prevent coalescence. Emulsification requiring very little input energy, minimization of the phase inversion temperature involves destabilization through contraction of local interfacial regions and therefore increasing the ease of emulsion. For emulsification to occur, it is necessary for the interfacial structure to have no resistance to surface shearing. In the case of self-emulsifying systems, the free energy required to form the emulsion is either very low and positive, or negative (then, the emulsification process occurs spontaneously).\cite{20}
Formulation variables and potential components

Any successful formulation of SNEDDS/SMEDDS depends on the thorough understanding of the spontaneous self-emulsification process and also on the physicochemical and biological properties of the components used for the construction of SNEDDS/SMEDDS. Process parameters mainly influencing the phenomenon of self-emulsification and also affects the size and bioavailability of these SNEDDS/SMEDDS:

1. Solubility of the drug in lipid/surfactant blends.
2. The physicochemical nature and concentration of oily phase, surfactant and co-emulsifier or co surfactant.
3. The ratio of the components, especially oil-to-surfactant ratio.
4. The temperature and pH of the aqueous phase where emulsification occurs.
5. Physicochemical properties of the drug, such as hydrophilicity/lipophilicity, pKa and polarity.
6. Acceptability of the SNEDDS/SMEDDS components for the desired route of administration is also very important.\(^{[20]}\)

Solid Self-Microemulsifying Drug Delivery System (S-SMEDDS) and solid self-nanoemulsifying drug delivery system (S-SNEDDS)

SMEDDS/SNEDDS mainly exist in two forms either liquid or solid form. Most of the SMEDDS/SNEDDS are limited to liquid dosage forms, because many excipients used in SMEDDS/SNEDDS are not solids at room temperature.\(^{[21]}\) But apart from that, liquid SMEDDS/SNEDDS when filled in capsules, few issues takes place such as the incompatibility of components with the capsule shell when kept for long term, precipitation of drugs during fabrication and storage at low temperature, critical method of production compared to others and useless for hydrophobic drugs that can undergo pH catalyzed or solution state degradation such as hydrolytic degradation at accelerated conditions of storage (hence, chemical stability of drugs in SMEDDS/SNEDDS needs to be studied at accelerated conditions).\(^{[22]}\)

Solid dosage form such as dry powder, tablets etc of SMEDDS/SNEDDS can be obtain by converting liquid SMEDDS/SNEDDS into solid SMEDDS/SNEDDS. The basic purpose to formulate SMEDDS/SNEDDS in a solid form is to surmount the disadvantages of liquid SMEDDS/SNEDDS with convenience of solid oral dosage forms.\(^{[18]}\)
Solidification techniques for transforming liquid/semisolid SMEDDS to S-SMEDDS

1. Capsule filling with liquid and semisolid self-emulsifying formulations

Many techniques are offered to convert conventional liquid SNEDDS and SMEDDS into solid form such as spray drying, adsorptions to solid carriers, spray cooling, melt extrusion, melt granulation, supercritical fluid based methods and high pressure homogenization. The resulting powder mixed with suitable excipients before compression into tablets. Solid SNEDDS and SMEDDS enhanced the bioavailability due to the presence of porous carriers and also show stability which is an important factor. The overall drug consumption and side-effects can be lowered by depositing the active agent in the morbid region only and in no higher dose than needed. This highly selective approach reduces the systemic side effects to a great extent.[21]

2. 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, forming dry particles under controlled temperature and airflow conditions. Such particles can be further prepared into tablets or capsules. The atomizer, the temperature, the most suitable airflow pattern and the drying chamber design are selected according to the drying characteristics of the product and powder specification.

3. Adsorption to solid carriers

Free flowing powders may be obtained from liquid SME formulations by adsorption to solid carriers. The adsorption process is simple and just involves addition of the liquid formulation onto carriers by mixing in a blender. The resulting powder may then be filled directly into capsules or, alternatively, mixed with suitable excipients before compression into tablets. A significant benefit of the adsorption technique is good content uniformity. A formulation of Liquid SMEDDS which is converted to Solid SMEDDS using Malto dextrin as a solid carrier was represented in Fig.4. SMEDDS can be adsorbed at high levels (up to 70% (w/w)) onto suitable carriers. Solid carriers can be micro porous inorganic substances, high surface-area colloidal inorganic adsorbent substances, cross-linked Polymers or Nanoparticle adsorbents, for example, silica, silicates, magnesium trisilicate, magnesium hydroxide, talcum.[21]
4. Solid carriers
These solid carriers have the property to absorb liquid/semisolid formulation as SES. It is a simple procedure, where SES is incorporated into a free-flowing powder material which has adsorption quality. The mixture is uniformly adsorbed by mixing in a blender. This solid mixture is filled into capsule or added to more excipient before compression into tablets. The above mixture is solidified to powder forms using three kinds of adsorbents: microporous calcium silicate (Florite RE), magnesium aluminum silicate (Neusilin US2) and silicon dioxide (Sylysia 320).

Different approaches for the dosage form development of solid-smedds and solid-snedds

1. Dry emulsion
Dry emulsions are powdered solid dosage forms in which suddenly emulsify occurs in vivo or with the expansion of water. It can be beneficial for further preparation of tablets and capsules. Self-micro and self-nano emulsifying dry emulsion formulations are generally prepared from oil/water (O/W) emulsions containing a solid carrier (lactose, maltodextrin, etc.) in the aqueous phase acquired by rotary evaporation, emulsifiable glass system, freeze drying, and spray drying.

2. Self-micro and self-nano emulsifying Capsules
Solid SMEDDS and solid SNEDDS are arranged by different systems such as dry emulsion can be filled into capsule shells. This can overcome the problem of physical incompatibility of liquid SMEDDS and liquid SNEDDS with the capsule shell. If semi-solid excipients are used in the formulation, they are firstly melted and then filled into capsules. Contents of the capsule then solidify at room temperature.[21]

3. Self-micro and self-nano emulsifying sustained/controlled-release tablets
For SME tablets, combinations of lipids and surfactants have presented novel approach researchers have been widely focus on this newer dosage forms. In their study, colloidal silicon dioxide (Aerosil 200), Neusilin and Fujicalin can select as a gelling agent for the oil-based systems, which served the dual purpose of reducing the amount of required solidifying excipients and aiding in slowing down of the drug release. For example; SE tablets may increase its penetration efficacy through the GI mucosal membranes, potentially reducing GI bleeding. The resultant SME/SNE tablets consistently maintained a higher active
ingredient concentration in blood plasma over the same time frame compared with a non-emulsifying tablet.

4. **Self-micro and self-nano emulsifying pellets (SME/SNE)**
   Self-emulsifying pellets were prepared by wet granulation method. In this formulation, a binder solution containing an oil (mono and diglycerides), polysorbate 80 and drug were used in different proportion. This oil-surfactant mixture will stir then added to water to form Self-emulsifying system. After that, prepare granules from microcrystalline cellulose and lactose in a granulator. These binder solutions were sprayed on to the granules and pellets were formed by increasing the speed of the granulator. Pellets were able to generate smaller droplets with respect to corresponding emulsions.\[^{18}\]

5. **Self- micro and self-nano emulsifying solid dispersions**
   Conventional solid dispersions could increase the dissolution rate and bioavailability of poorly water-soluble drugs, some manufacturing difficulties and stability problems raised. Excipients have the potential to increase further the absorption of poorly water-soluble drugs relative to previously used PEG solid dispersions and may also be filled directly into hard gelatin capsules in the molten state, thus obviating the former requirement for milling and blending before filling. SME/SNE excipients like Gelucire1 44/14, Gelucire150/02, Labrasol1, Transcutol1 and TPGS (tocopheryl polyethylene glycol 1000 succinate) have been widely incorporated in this field.\[^{23}\]

6. **Self- micro and self-nano emulsifying suppositories**
   Some researchers found that S-SMEDDS/S-SNEDDS could increase not only GI adsorption but also rectal/vaginal adsorption. For example Glycyrrhizin, which is given by the oral route, barely achieves therapeutic plasma concentrations, can obtain satisfactory therapeutic levels for chronic hepatic diseases by either vaginal or rectal SME suppositories.\[^{24}\]

7. **Self- micro and self-nano emulsifying implants**
   As an example, 1,3-bis(2-chloroethyl)-1- nitrosourea is a chemotherapeutic agent used to treat malignant brain tumors. However, its effectiveness was hindered by its short half-life. In order to enhance its stability compared with that released from Poly (d,l-lactide-co-glycolide) (PLGA) wafer implants, SMES/SNES was formulated. Such wafers had higher in vitro antitumor activity and were less susceptible to hydrolysis.
8. Self-emulsifying beads
Porous polystyrene beads were used for delivering self-emulsifying formulations. The formulation is incorporated into microchannels of the bead through capillary action. The beads were prepared by copolymerizing styrene and divinyl benzene.

9. Self-emulsifying nanoparticles
Self-emulsifying nanoparticles can be formulated by using solvent injection technique, wherein the excipients and medication are softened together and infused into a nonsolvent. The nanoparticles can be isolated by centrifugation and lyophilization.

10. Sponges carrying self-micro and self-nano emulsifying Drug Delivery Systems
This is a novel approach for the formulation of SMEDDS/SNEDDS—their incorporation in sponges made from a hydrophilic regular polymer. The nanosponge structures were concentrated on with examining electron microscopy and little edge X-beam diffusing. The oil beads survived the drying procedure and SMEDDS/SNEDDS were available as 9 nm-sized objects in the dried sponges.

11. Self-Microemulsifying Mouth Dissolving Film
The SMMDF was break inside for 20 s after mixing with water, discharged totally at 5 min in the disintegration medium and accomplished micro-emulsion molecule size of 28.81 ± 3.26 nm. Solid state structure of the SMMDF was performed by SEM, DSC and X-ray powder diffraction. It is recommend that the SMMDF is another promising dose structure which demonstrates the remarkable attributes of accommodation, speedy onset of activity and upgraded oral bioavailability of poorly water-soluble drugs.[18]

DIFFERENCE BETWEEN SMEDDS AND SNEDDS

<table>
<thead>
<tr>
<th>Features</th>
<th>SMEDDS</th>
<th>SNEDDS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Self micro-emulsifying drug delivery system</td>
<td>Self nano-emulsifying drug delivery system</td>
</tr>
<tr>
<td>Size range of globules</td>
<td>Size ranges from 100-200 nm</td>
<td>Size ranges from 50-100 nm</td>
</tr>
<tr>
<td>Appearance</td>
<td>Appearance of dispersion is optically clear to translucent</td>
<td>Appearance of dispersion is optically clear</td>
</tr>
<tr>
<td>Stability</td>
<td>Thermodynamically stable system</td>
<td>Thermodynamically unstable and kinetically stable</td>
</tr>
<tr>
<td>Order of mixing</td>
<td>Surfactant should be mixed with oily phase followed by titration of the obtained mixture with the aqueous phase</td>
<td>The order of mixing the components does not affect formation.</td>
</tr>
</tbody>
</table>
Concentration

<table>
<thead>
<tr>
<th>Type of system</th>
<th>In both the system drug is given in solubilized form but, micro system is one phasic with swollen micells i.e., equilibrium systems</th>
<th>Nanoemulsion is true emulsion i.e., non-equilibrium systems with a spontaneous tendency to separate into the constituent phases.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy required</td>
<td>Large amount of energy is required for preparation as compared to nanoemulsion</td>
<td>Less energy required for preparation.</td>
</tr>
</tbody>
</table>

Characterization of SMEDDS/SNEDDS

The primary means of self-emulsification assessment is visual evaluation. The efficiency of self-emulsification could be estimated by determining the rate of emulsification, droplet-size distribution and turbidity measurements.

1. Visual assessment

This may provide important information about the self-emulsifying and micro emulsifying property of the mixture and about the resulting dispersion.

2. Turbidity Measurement

This is to identify efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time.

3. 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 stability of the emulsion. Photon correlation spectroscopy, microscopic techniques or a Coulter Nanosizer are mainly used for the determination of the emulsion droplet size. The reduction of the droplet size to values below 50 μm leads to the formation of SMEDDSs, which are stable, isotropic and clear o/w dispersions. [25]

4. Zeta Potential Measurement

This is used to identify the charge of the droplets. In conventional SEDDSs, the charge on an oil droplet is negative due to presence of free fatty acids.

5. 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 50rpm provided gentle agitation. The in vitro performance of the formulation 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 slightly oily appearance that is slow to emulsify (longer than 2 min).

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

6. **Drug content**
Drug from preweighed SEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract was analyzed by suitable analytical method against the standard solvent solution of drug.[26]

**Application**
SMEDDS/SNEDDS formulation is composed of lipids, surfactants, and cosolvents. The system has the ability to form an oil-in-water emulsion when dispersed by an aqueous phase under gentle agitation. SMEDDSs/SNEDDS present drugs in a small droplet size and well-proportioned distribution, and increase the dissolution and permeability.

**CONCLUSION**
Currently, SEDDS (include SMEDDS and SNEDDS) are in focus for developing formulations of poorly water soluble drugs. However, a considerable gap exists between the need for lipid-based drug delivery systems and the available marketed products of SMEDDS/SNEDDS. Various attempts have been made to overcome the problems associated with liquid SMEDDS/SNEDDS. Most of the marketed SMEDDS/SNEDDS formulations are in soft gelatin capsule which manifests handling issues and also increases cost of the product. Thus, formulating solid SMEDDS/SNEDDS could minimize handling issues, decrease cost of product and would overcome stability problem of liquid product. Also, these formulations should be designed to work in harmony with the physiological environment. Such attempts
will ensure complete exploration or usage of this potential drug delivery system especially for poorly soluble drug.

REFERENCES


