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# **REVIEW ARTICLE**

# Self-Microemulsifying Drug Delivery System (SMEDDS): A Novel Approach for Enhancement of Oral Bioavailability of Poorly Soluble Drugs

Panola R, Mishra A\*, Chauhan CS, Kansara H

*B. N. Institute of Pharmaceutical Sciences, Udaipur (Rajasthan)-313002, India.* Manuscript No: IJPRS/V4/I2/00110, Received On: 28/05/2015, Accepted On: 07/06/2015

#### ABSTRACT

The ability of Self Micro-emulsifying Drug Delivery Systems (SMEDDS) is to improve solubility, dissolution rate and bioavailability of a poorly water-soluble drug as there is steady increase in number of pharmacological active poorly water soluble compound. For the improvement of bio-availability of drugs with such properties, various technological strategies are reported in the literature including solid dispersions, cyclodextrines complex formation, or micronization, and different technologies of drug delivery systems. Including these approaches Self Micro-emulsifying Drug Delivery Systems (SMEDDS) have gained exposé for enhancement of oral bio-availability with reduction in dose. SMEDDS are isotropic mixtures of oil, surfactants, solvents and co-solvents/surfactants can be used for the design of formulations in order to improve the oral absorption of highly lipophilic drug compounds. It can be orally administered in soft or hard gelatin capsules. These systems form fine emulsions (or micro-emulsions) in gastro-intestinal tract (GIT), with mild agitation provided by gastric mobility.

#### **KEYWORDS**

Self Micro-emulsifying Drug Delivery Systems, Bioavailability enhancement

#### **INTRODUCTION**

The oral route has been the major and one of the favorite routes of drug delivery for chronic treatment of many diseases. Oral drug delivery system is the most cost-effective and leads the world wide drug delivery market in present time near about 40% of the drugs are lipophilic in nature. The lipid based formulation had offered variety of systems like solution, suspension, emulsion, solid dispersion, self emulsifying system for this type of drugs.<sup>1</sup>

SMEDDS formulations can be simple binary systems: lipophilic phase and drug, or lipophilic phase, surfactant and drug.

The formation of a SMEDDS requires the use of a co-surfactant to generate a micro emulsion. SMEDDS formulations are characterized by in vitro lipid droplet sizes of 200 nm-5 mm and the dispersion has a turbid appearance.<sup>2</sup> Self Microemulsifying Drug Delivery Systems (SEDDS) are isotropic mixtures of drug, lipids and surfactants, usually with one or more Hydrophilic co-solvents or co emulsifiers. Upon mild agitation followed by dilution with aqueous media, these systems can form fine (oil in water) emulsion instantaneously. SMEDDS 'is a term, typically producing emulsions with a droplet size ranging from a few nanometers to several microns. Self-micro emulsifying Drug delivery systems'(SMEDDS) indicates the formulations forming transparent micro emulsions with oil droplets ranging between 100 and 250 nm. Selfnano-emulsifying drug delivery system's a recent

<sup>\*</sup>Address for Correspondence: Dr. Amul Mishra B. N. Institute of Pharmaceutical Sciences, Udaipur (Rajasthan)-313002, India. E-Mail Id: amulnmishra@gmail.com

term construing the globule size range less than 100 nm<sup>3</sup>. In-water emulsions when introduced into an aqueous phase under gentle agitation. SMEDDS can be administered orally in soft or hard gelatin capsules and form fine, relatively stable oil-in-water emulsions upon aqueous dilution<sup>4</sup>.



Figure 1: BCS classification system of drugs

### **Composition of SMEDDS**

The self-emulsifying process is depends on<sup>5</sup>

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

#### Oils

Oils can solubilize the lipophilic drug in a specific amount. It is the most important excipients because it can facilitate selfemulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract. Long-chain triglyceride and medium chain triglyceride oils with different degrees of saturation have been used in the design of SMEDDS. Modified or hydrolyzed vegetable oils have contributed widely to the success of SMEDDS owing to their formulation and physiological advantages<sup>6</sup>. Novel semi synthetic medium-chain triglyceride oils have

surfactant properties and are widely replacing the regular medium- chain triglyceride<sup>7</sup>.

#### Surfactant

Non-ionic surfactants with high hydrophiliclipophilic balance (HLB) values are used in formulation of SMEDDS (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore, etc.). The usual surfactant strength ranges between 30-60% w/w of the formulation in order to form a stable SEDDS. Surfactants have a high HLB and hydrophilicity, which assists the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds. This can prevent precipitation of the drug within the GI lumen and for prolonged existence of drug molecules<sup>8</sup>. Emulsifiers derived from natural sources are expected to be safer than synthetic ones and are recommended for SDLF (self dispersed lipid formulation). Non-ionic surfactants are known to be less toxic compared to ionic surface-active agents, but they may cause moderate reversible changes in intestinal wall permeability. Amemiya et al. proposed a new vehicle based on a fine emulsion using minimal surfactant content (3%) to avoid the potential toxicological problems associated with high surfactant concentration. The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of Self Micro-emulsifying Drug (SMEDDS).Formulations Delivery Systems consisting only of the surfactant mixture may form emulsions or micro emulsions (when surfactants exhibit different low and high HLB), micelle solution or, in some particular cases, niosomes, which are non-ionic, surfactant based bilayer vehicles.

## Co- solvents

Cosolvents like diehyleneglycol monoethyle ether (transcutol), propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, tetra hydrofurfuryl alcohol polyethylene Glycol ether (Glycofurol), etc., may help to dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base. These solvents sometimes play the role of the cosurfactant in the micro emulsion systems.



Figure 2: Ingredients used in the formulation of SMEDDS



Figure 3: Mechanism of SMEDDS

#### **Formulation of SMEDDS**

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 encapsulation in hard or soft gelatin or mixtures which disperse to give fine colloidal emulsions.<sup>9</sup>

The following should be considered in the formulation of a SEDDS:

The solubility of the drug in different oil, surfactants and co-solvents. The selection of oil, surfactant and cosolvent based on the solubility of the drug and the preparation of the phase diagram.<sup>10</sup>

The preparation of SMEDDS formulation by dissolving the drug in a mixture of oil, surfactant and co-solvent.

The addition of a drug to a SMEDDS is critical because the drug interferes with the selfemulsification process to a certain extent, which leads to a change in the optimal oil–surfactant ratio. So, the design of an optimal SMEDDS requires preformulation-solubility and phasediagram studies. In the case of prolonged SMEDDS, formulation is made by adding the polymer or gelling agent.<sup>11</sup>



Figure 4: Self emulsifying therapeutic systems

#### **Techniques of SMEDDS**

## 1. Spray Congealing

The melted droplets are atomized into cooling chamber, which will congeal and crystallize into

spherical solid particle that will fall down in the chamber and collected as fine powder.<sup>12</sup>

# 2. Spray Drying

Spray drying is referred as a process by which small lot of solution is sprayed into a hot air chamber to evaporate the volatile fraction.<sup>13</sup>

## 3. Supercritical Fluid Based Method<sup>14</sup>

Lipids may be used in supercritical fluid based method either for coating of drug particle or for producing solid dispersion.

## 4. Melt Granulation

Melt granulation or pelletization is one step process allowing the transformation of a powder mix containing the drug into granules or spheronized pellets.<sup>15</sup>

#### 5. Solid Lipid Nanoparticles and Nanostructures Lipid Carriers

SLN and NLC are two types of submicron size particles about 50-1000nm composed of physiologically tolerated lipid components. They are produced by high-pressure homogenization of the solid matrix and drug with an aqueous solution.<sup>16</sup>



Figure 5: Mechanism of Self-Emulsification

# Mechanism of Self-Emulsification

The process by which self-emulsification takes place is not yet well understood, however, according to Reiss, self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion. In addition, the free energy of a conventional emulsion formation is a direct function of the energy requires creating a new surface between the two phases and can be described by equation

$$\Delta G = \sum_{i} N_{i} \pi r_{i}^{2} \sigma$$

Where, **G** is the free energy associated with the process (ignoring the free energy of mixing), **N** is the number of droplets of radius **r**, and **S** represents the interfacial energy.

With time, the two phases of the emulsion will tend to separate, in order to reduce the interfacial area, and subsequently, the free energy of the systems.<sup>17</sup>

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. Emulsification requiring very little input energy involves destabilization through contraction of local interfacial regions. For emulsification to occur, it is necessary for the interfacial structure to have no resistance to surface shearing.<sup>18</sup> 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).



Figure 6: Drug transit in SMEDDS

#### Advantages of SMEEDS<sup>19,20</sup>

- Quick Onset of Action
- Reduction in the Drug Dose
- Ease of Manufacture & Scale-up
- Improvement in oral bioavailability
- Inter-subject and Intra-subject variability and food effects
- Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT
- No influence of lipid digestion process
- Increased drug loading capacity

### **Disadvantages of SMEDDS**<sup>20</sup>

- Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.
- 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.
- The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which GIT.

#### **Need of SMEDDS**

SMEDDS are promising approach for oral delivery of poorly water-soluble compounds. It can be achieved by pre-dissolving the compound in a suitable solvent and fill the formulation into capsules. The oral drug delivery of hydrophobic drugs can be made possible by SMEDDS. The main benefit of this approach is that predissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract. However, a 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 favors the drug remaining in the lipid droplets.<sup>21</sup>



Figure 7: Drug release via SMEDDS

## Evaluation

## Thermodynamic Stability Studies

stability of a The physical lipid-based formulation is also important to its performance, which can produce adverse effect in the form of precipitation of the drug in the excipients matrix. In addition, the poor physical stability of the formulation can lead to phase separation of the excipients, which affects not only formulation performance, as well as visual appearance of incompatibilities formulation. In addition. between the formulation and the gelatin capsules shell can lead to brittleness or deformation,

delayed disintegration, or incomplete release of drug.

For thermodynamic stability studies we have performed three main steps, they are-

1. Heating cooling cycle: Six cycles between refrigerator temperature  $(4^{0}C)$  and  $45^{0}C$  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.

2. Centrifugation: Passed formulations are centrifuged thaw cycles between  $21^{\circ}C$  and  $+25^{\circ}C$  with storage at each temperature for not less than 48 h is done at 3500 rpm for 30 min. Those formulations that does not show any phase separation are taken for the freeze thaw stress test.

3. Freeze thaw cycle: Three freeze for the formulations. Those formulations passed this test

Show good stability with no phase separation, creaming, or cracking.<sup>22</sup>

### Dispersibility Test

The efficiency of self-emulsification of oral nano or micro emulsion is assessed by using a standard USP XXII dissolution apparatus 2 for dispersibility test. One millilitre of each formulation was added in 500 mL of water at 37  $\pm$  1<sup>0</sup>C. A standard stainless steel dissolution paddle is used with rotating speed of 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 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 nano emulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SMEDDS formulation.<sup>22</sup>

#### Turbidimetric Evaluation

Nephelo-turbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of Self emulsifying system is added to fixed quantity of suitable medium (0.1N hydrochloric acid) under continuous stirring (50 rpm) on magnetic hot plate at appropriate temperature, and the increase in turbidity is measured, by using a turbid meter. 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)<sup>23,24</sup>

## 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 systems should not be too thick. The rheological properties of the micro emulsion are evaluated by Brookfield viscometer. This viscosities determination conform whether the system is w/o or o/w. If the system has low viscosity then it is o/w type of the system and if a high viscosity then it is w/o type of the system.<sup>23,24</sup>

# Droplet Size Analysis and 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  $25^{\circ}$ 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.<sup>23,24</sup>

#### **Refractive Index and Percent Transmittance**

Refractive index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by refracto-meter by putting a drop of solution on slide and it comparing it with water (1.333). The percent transmittance of the system is measured particular wavelength at using UV spectrophotometer by using distilled water as blank. If refractive index of system is similar to the refractive index of water (1.333) and formulation have percent transmittance > 99percent, then formulation have transparent nature.

#### Electro Conductivity Study

The SMEDD system contains ionic or non-ionic surfactant, oil, and water. This test is performed for measurement of the electro conductive nature of system. The electro conductivity of resultant system is measured by electro conductometer. In conventional SMEDDSs, the charge on an oil droplet is negative due to presence of free fatty acids.<sup>25</sup>

#### In- Vitro Diffusion Study

*In vitro* diffusion studies are carried out to study the drug release behavior of formulation from liquid crystalline phase around the droplet using dialysis technique.<sup>23</sup>

#### Drug Content

Drug from pre-weighed SMEDDS 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.<sup>26</sup>

#### Factors which Affect SMEDDS<sup>27</sup>

#### Polarity of the Lipophilic Phase

The polarity of the lipid phase is one of the main factors that govern the drug release from the micro-emulsions. The polarity of the droplet is governed by the HLB, the chain length and degree of unsaturation of the fatty acid, the molecular weight of the hydrophilic portion and the concentration of the emulsifier. In fact, 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. This is confirmed by the observations of Sang-Cheol Chi, who observed that the rate of release of idebenone from SMEDDS is dependent upon the polarity of the oil phase used. The highest release was obtained with the formulation that had oil phase with highest polarity.

#### Nature and Dose of the Drug

Drugs which are administered at very high dose are not suitable for SMEDDS unless they have extremely good solubility in at least one of the components of SMEDDS, preferably lipophilic phase. The drugs which have or less solubility in water and lipids are most difficult to deliver by SMEDDS. The ability of SMEDDS to maintain the drug in solubilized form is greatly influenced by the solubility of the drug in oil phase. As mentioned above if surfactant or co-surfactant is contributing to the greater extent in drug solubilization then there could be a risk of precipitation, as dilution of SMEDDS will lead to lowering of solvent capacity of the surfactant or Equilibrium co-surfactant. solubility measurements can be carried out to anticipate potential cases of precipitation in the gut. However, crystallization could be slow in the solubilizing and colloidal stabilizing environment of the gut. Pouton's study reveal that such formulations can take up to five days to reach equilibrium and that the drug can remain in a super-saturated state for up to 24 hours after the initial emulsification event. It could thus be argued that such products are not likely to cause precipitation of the drug in the gut before the drug is absorbed, and indeed that super-saturation could actually enhance absorption by increasing the thermodynamic activity of the drug. There is a clear need for practical methods to predict the fate of drugs after the dispersion of lipid systems in the gastro-intestinal tract.

#### **Dosage Form Development of SMEDDS**

#### Dry Emulsions

Dry emulsions are powders from which emulsion spontaneously occurs in vivo or when exposed to an aqueous solution. Dry emulsions can be useful for further preparation of tablets and capsules. Dry emulsion formulations are typically prepared from oil/ water (O/W) emulsions containing a solid carrier (lactose, maltodextrin, and so on) in the aqueous phase by rotary evaporation<sup>28</sup>, freeze-drying<sup>29</sup> or spray drying.

Myers and Shively obtained solid state glass emulsions in the form of dry foam 'by rotary evaporation, with heavy mineral oil and sucrose. Such emulsifiable glasses have the advantage of not requiring surfactant. In freeze-drying, a slow cooling rate and the addition of amorphous cryo protectants have the best stabilizing effects, while heat treatment before thawing decreases the stabilizing effects. The technique of spray drying is more frequently used in preparation of dry emulsions. The O/W emulsion was formulated and then spray dried to remove the aqueous phase. The most exciting finding in this field ought to be the newly developed enteric-coated dry emulsion formulation, which is potentially applicable for the oral delivery of peptide and protein drugs. This formulation consisted of a surfactant, a vegetable oil, and a pH-responsive polymer, with lyophilization used<sup>30</sup>. Recently, Cui et al. prepared dry emulsions by spreading liquid O/W emulsions on a flat glass, then dried and triturated to powders<sup>31</sup>.

## Self Emulsifying Capsules

After administration of capsules containing conventional liquid SE formulations, micro emulsion droplets form and subsequently disperse in the GI tract to reach sites of absorption.

However, if irreversible phase separation of the micro emulsion occurs, an improvement of drug absorption cannot be expected. For handling this problem, sodium dodecyl sulfate was added into the SE formulation<sup>41</sup>. With the similar purpose, the super-saturable SEDDS was designed, using a small quantity of HPMC (or other polymers) in the formulation to prevent precipitation of the generating and maintaining drug by a supersaturated state in vivo. This system contains are duced amount of a surfactant.

Thereby minimizing GI side effects.<sup>33,34</sup> Besides liquid filling, liquid SE ingredients also can be filled into capsules in a solid or semisolid state obtained by adding solid carriers (adsorbents, polymers, and so on). As an example, a solid PEG matrix can be chosen. The presence of solid PEG neither interfered with the solubility of the drug, nor did it interfere with the process of self micro emulsification upon mixing with water.<sup>35,36</sup> Oral administration of SE capsules has been found to enhance patient compliance compared with the previously used parenteral route. For instance, low molecular weight heparin (LMWH) used for the treatment of venous thrombo-embolism 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: micro porous calcium silicate (FloriteTM RE): magnesium aluminum silicate (NeusilinTM US2) and silicon dioxide (SylysiaTM 320). Eventually these solids were filled into hard capsules.<sup>37</sup> In another study, such adsorbents were also applied to prepare SE tablets of gentamicin that, in clinical use, was limited to administration as injectable or topical dosage forms.<sup>38</sup>

## Self Emulsifying Sustained/Controlled Release Tablets

Combinations of lipids and surfactants have presented great potential of preparing SE tablets that have been widely researched and evaluated the effect of some processing parameters (colloidal silicates-X1, magnesium stearate mixing time— X2, and compression force—X3) on hardness and coenzyme Q10 (CoQ10) dissolution from tablets of eutectic-based SMEDDS. The optimized conditions (X1 =1.06%, X2 = 2 min, X3 = 1670 kg) were achieved by a face-centered cubic design<sup>39</sup>. In order to reduce significantly the amount of solidifying excipients required for transformation of SMEDDS into solid dosage forms, a gelled SMEDDS has been developed. In their study, colloidal silicon dioxide (Aerosil 200) was selected 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<sup>40</sup>. SE tablets are of great utility in obviating adverse effect, as disclosed by Schwarz in a patent. Inclusion of indomethacin (or other hydrophobic NSAID), for example, into SE tablets may increase its penetration efficacy through the GI mucosal membranes, potentially reducing GI bleeding. In these studies, the SES was composed of glycerol monolaurate and Tyloxapol TM (a copolymer of alkyl phenol and formaldehyde).

# Self Emulsifying Sustained/Controlled Release Pellets

Pellets, as a multiple unit dosage form, possess many advantages over conventional solid dosage forms, such as flexibility of manufacture, reducing intrasubject and intersubject variability of plasma profiles and minimizing GI irritation without lowering drug bioavailability<sup>40</sup>. Thus, it is very appealing to combine the advantages of pellets with those of SMEDDS by SE pellets. The prepared SE controlled release pellets by incorporating drugs into SES that enhanced their rate of release, and then by coating pellets with a water-insoluble polymer that reduced the rate of drug release. Pellets were prepared by extrusion/ spheronization and contained two water-insoluble model drugs (methyl and propyl parabens); SES contained monodiglycerides and Polysorbate 80. There is another report that SE sustained-release matrix pellets could be successfully formulated with glycerylpalmito-stearate (Gelucire 54/02) and glyceryl behenate (Gelucire 70/02)<sup>41</sup>.

# Self Emulsifying Solid Dispersions

Although solid dispersions could increase the dissolution rate and bioavailability of poorly manufacturing water-soluble drugs, some difficulties and stability problems existed. Serajuddin pointed out that these difficulties could be surmounted by the use of SE excipients.<sup>42,43</sup> These 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.<sup>44</sup> SE excipients like Gelucire1 44/14, Gelucire1 50/02, Labrasol1, Transcutol and TPGS (tocopheryl polyethylene glycol 1000 succinate) have been widely used in this field.<sup>45</sup>

# Self Emulsifying Beads

In an attempt to transform SES into a solid form with minimum amounts of solidifying excipients, Patil and Paradkar investigated loading SES into the micro-channels of porous polystyrene beads (PPB) using the solvent evaporation method. PPB with complex internal void structures is typically produced by copolymerizing styrene and divinyl benzene. They are inert, stable over a wide pH range and to extreme conditions of This research temperature and humidity. concluded that PPB was potential carriers for solidification of SES, with sufficiently high SES to PPB ratios required to obtain solid form. Geometrical features, such as bead size and pore architecture of PPB, were found to govern the loading efficiency and in vitro drug release from SES loaded PPB.<sup>46</sup>

# Self Emulsifying Sustained Release Microspheres

Zedoary turmeric oil (ZTO; a traditional Chinese medicine) exhibits potent pharmacological actions suppressive, including tumour antibacterial, and antithrombotic activity. With ZTO as the oil phase, prepared solid SE sustained-release microspheres using the quasi emulsion solvent-diffusion method of the spherical crystallization technique. ZTO release behavior could be controlled by the ratio of hydroxylpropyl methylcellulose acetate succinate to Aerosil 200 in the formulation. The plasma concentration- time profiles were achieved after oral administration of such microspheres to rabbits, with a bioavailability of 135.6% with respect to the conventional liquid SMEDDS.<sup>47</sup>

# Self Emulsifying Nanoparticles

Nanoparticle techniques have been useful in the production of SE nanoparticles. Solvent injection is one of these techniques. In this method, the lipid, surfactant, and drugs were melted together, and injected drop wise into a stirred non-solvent. The resulting SE nanoparticles were thereafter filtered out and dried. These approach yielded nanoparticles (about 100 nm) with a high drug loading efficiency of 74%.<sup>48</sup>

# Self Emulsifying Suppositories

Some investigators proved that S-SMEDDS could increase not only GI adsorption but also rectal/vaginal adsorption. Glycyrrhizin, which, by the oral route, barely achieves therapeutic plasma concentrations, can obtain satisfactory therapeutic levels for chronic hepatic diseases by either vaginal or rectal SE suppositories. The formulation included glycyrrhizin and a mixture of a C6–C18 fatty acid glycerol ester and a C6–C18 fatty acid macrogol ester.<sup>50</sup>

# Self-Emulsifying Implants

Research into SE implants has greatly enhanced the utility and application of S-SMEDDS. As an example, 1, 3-bis (2-chloroethyl) -1-nitrosourea (carmustine, BCNU) is a chemotherapeutic agent used to treat malignant brain tumors. However, its effectiveness was hindered by its short half-life. Loomis invented copolymers having a bioresorbable region, a hydrophilic region and at least two cross-linkable functional groups per polymer chain. Such copolymers show SE property without the requirement of an emulsifying agent. These copolymers can be used as good sealants for implantable prostheses.<sup>51</sup>

# Applications<sup>19</sup>

# Improvement in Solubility and Bioavailability

If drug is formulated in SMEDDS, then it increases the solubility because it circumvents the dissolution step in case of Class-Π drug (Low solubility/high permeability). Ketoprofen, a moderately hydrophobic non steroidal antiinflammatory drug (NSAID), it is a drug of choice for sustained release formulation but it has produce the gastric irritation during chronic therapy. Along with this due to its low solubility, ketoprofen shows incomplete release from sustained release formulations. It is reported that the complete drug release from sustained release formulations containing ketoprofen in nano crystalline form. Different formulation

approaches that have been achieved sustained release, decrease the gastric irritation, and increase the bioavailability, of ketoprofen include preparation of matrix pellets of nano-crystalline sustained release ketoprofen ketoprofen, microparticles<sup>23</sup> and formulations<sup>23</sup>, floating oral ketoprofen systems, and transdermal systems of ketoprofen.<sup>25</sup> 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 increase the solubility of drug and minimizes the gastric irritation. Also incorporation of gelling agent in SMEDDS sustained the release of Ketoprofen. 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 Cmax is observed with many drugs when presented in SMEDDS.

# Protection against Biodegradation

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. Many drugs are degraded in physiological system, may be because of acidic pH in stomach, hydrolytic degradation, or enzymatic degradation etc. Such drugs when presented in the form of SMEDDS can be well protected against these degradation processes as liquid crystalline phase in SMEDDS might be an act as barrier between degradation environment and the drug

# **Future Trend**

For the formulation development of poorly water soluble drug in the future, there is now method used for converting liquid/semi-solid SMEDDS and SMEDDS formulations into powders and granules, which can then be processed into conventional 'powder-fill' capsules or even Self-Micro Emulsifying Drug Delivery System (SMEDDS): A Novel Approach for Enhancement of Oral Bioavailability of Poorly Soluble Drugs

compressed into tablets. Hot melt granulation is a technique for producing granules or pellets, and by using a waxy solubilizing agent as a binding agent, up to 25% solubilizing agent can be incorporated in a formulation. There is also increasing interest in using inert adsorbents, such as the Neusilin products for converting liquids into powders – which can then be processed into powder fill capsules or tablet. Oral delivery of poorly water-soluble compounds is to predissolve the compound in a suitable solvent and fill the formulation into capsules.

The main advantage of this approach is that predissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract. However, a potential problem is that the drug may precipitate out of solution when the formulation disperses in the GI tract.

The pharmaceutical product formulated as self emulsifying systems are:

Drug name	Compound	Dosa <mark>ge</mark> form	Company
Neural	Cyclosporine	Soft gelatin capsule	Novartis
Norvir	Ritonavir	Soft gelatin capsule	Abbot laboratories
Fortovase	Saquinavir	Soft gelatin capsule	Hoffmann- La Rocho Inc.
Solufen	Ibuprofen	Hard gelatin capsule	Sanofi- Aventis
Agenerase	Amprenavir	Soft gelatin capsule	Glaxosmit k line
Lipirex	Fenofibrate	Hard gelatin capsule	Sanofi- Aventis

Table 1: Pharmaceutical formulations



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