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A REVIEW ON SELF EMULSIFYING DRUG DELIVERY SYSTEMS

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Abstract: *The oral route is the preferred route for chronic drug therapy. Numerous potent lipophilic drugs exhibit low oral bioavailability due to their poor aqueous solubility properties (class II: low solubility and high permeability drugs).The most popular approach to increase the oral bioavailability of lipophilic drugs is the incorporation of the active lipophilic component into inert lipid vesicles such as oils, surfactant dispersions, self-emulsifying formulations, emulsions and liposomes. Most lipid based formulations are designed to deliver the entire dose in solution thereby bypassing the dissolution process in the gastro-intestinal tract, which has been recognized as one of the main prerequisite for the efficiency of these formulations. These systems often lead to improvement in the therapeutics index of the lipophilic drugs through increased solubilization and modification of their pharmacokinetic profiles. The present article gives information regarding composition, mechanism, characterization and factors affecting the SEDDS.*

Keywords: Self-emulsifying formulations, permeability, solubility, emulsions and therapeutic index.

1. Introduction

Self-emulsifying drug delivery systems (SEDDS) are mixtures of oils and surfactants, ideally isotropic, and sometimes containing co-solvents, which emulsify spontaneously to produce fine oil-in-water emulsions when introduced into aqueous phase under gentle agitation. Upon peroral administration, these systems form fine emulsions ("Self Emulsifying Formulations") or micro emulsion ("Self Micro Emulsifying Formulations") in gastro-intestinal tract (GIT) with mild agitation provided by gastric mobility. The spontaneous formation of emulsion advantageously presents the drug in a dissolved form, and the resultant small droplet size provides a large interfacial surface area. These characteristics result in faster drug release from emulsion in a reproducible manner, which can be designed further to make the release characteristics independent of the gastrointestinal physiology and the fed/fasted state of the patient. These formulations can be administered in soft or hard gelatin capsules, and will produce fine oil droplets/ micelle dispersion upon capsule disintegration and aqueous dilution [1].

Oral delivery of poorly water-soluble compounds is to pre-dissolve the compound in a suitable solvent and fill the formulation into capsules. The main benefit of this approach is that pre-dissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract. However, 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

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will favour the drug remaining in the lipid droplets. Another strategy for poorly soluble drugs is to formulate in a solid solution using a water-soluble polymer to aid solubility of the drug compound. For e.g., PVP K30 and PEG 6000 have been used for preparing solid solutions with poorly soluble drugs. One potential problem with this type of formulation is that the drug may favour a more thermodynamically stable state, which can result in the compound crystallizing in the polymer matrix [1, 2].

Therefore the physical stability of such formulations needs to be assessed using techniques such as differential scanning calorimetry or X-ray crystallography. In this type of cases SEDD system is a good option.

Advantages

- Enhanced oral bioavailability enabling reduction in dose of the drug
- More consistent temporal profiles of drug absorption
- Selective targeting of drug towards specific absorption window in GIT
- Protection of drug from the hostile environment in gut
- Control of delivery profiles
- Reduced variability including food effects
- Protection of sensitive drug substances
- High drug payloads (as the solubility of poorly water soluble drugs with intermediate partition coefficient ($2<\log p<4$) are typically low in natural lipids and much greater in amphiphilic surfactants, co-surfactants and co-solvents
- Ease of manufacture and scale up when compared to other bioavailability enhancement techniques like solid dispersions, liposomes and nanoparticles
- Emulsions are sensitive and metastable dispersed forms while SMEDDS are physically stable formulation that are easy to manufacture
- As compared with oily solutions, they provide a large interfacial area for partitioning of the drug between oil and water
- Fine oil droplets of these SEDDS would pass rapidly and encourage extensive distribution of the drug all the way through the GI tract, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substance and the gut wall
- For lipophilic drug compounds that exhibit dissolution rate limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood time profiles[3, 4].

Disadvantages

- Lack of good predicative *in-vitro* models for assessment of the formulations
- Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug
- High production costs

- Formulations containing several components become more challenging to validate
- Low drug incompatibility
- Drug leakage is possible, so it may allow less drug loading [3, 4].

2. Composition of SEDDS

Along with the active pharmaceutical ingredient, i.e., poorly soluble drugs, e.g., Itraconazole, nifedipine, vitamin E, simvastatin, ketoconazole, naproxen and carbamazepine, SEDDS are composed of the following excipients:

2.1. Lipid based excipients

Oils are the most important excipient because oil can solubilise the lipophilic drug in a specific amount and it can facilitate self-emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing the absorption from the GIT. Oils used in SEDDS formulations are mainly vegetable oils and vegetable oil derivatives [5].

2.1.1. Vegetable oils: Both long and medium chain triglyceride oils with different degrees of saturation have been used for the design of self-dispersing formulation.

E.g., Castor oil, coconut oil, corn oil, cotton seed oil, grape seed oil, olive oil and sesame oil.

2.1.2. Vegetable oil derivatives: Unmodified edible oils have poor ability to dissolve large amounts of hydrophobic drugs and their relative difficulty in efficient self-emulsification markedly reduces their use in SEDDS. In contrast, modified vegetable oils have contributed widely to the success of the above systems since they exhibit formulative and physiological advantages [5]. The modified vegetable oil derivatives are as follows:

- **Hydrogenated vegetable oils:** These are obtained by catalytic hydrogenation of the unsaturated bonds with nickel.
  E.g., Lubritab (hydrogenated castor oil) and hydrocote (hydrogenated sesame oil).

- **Partial glycerides:** These are the products of glycerolysis.
  E.g., Capmul (glycerylmonocaprylcaprate), geleol (glycerylmonosterate) and paceol (glycerylmonoleate).

- **Polyoxylglycerides:** Obtained by polyglycolysis of vegetable oils with PEG of certain molecular weight (varying from 200 to 2000 g/mol) under heating and in presence of an alkaline catalyst. Each polyoxylglyceride is composed of a definite mixture of mono, di and triglycerides and mono and diesters of PEG.
  E.g., Linoleylpolyoxylglycerides, caproylpolyoxylglycerides and steroylpolyoxylglycerides.

- **Ethoxylated glycerides:** These are derived from castor oil that is rich in ricinoleic acid and are widely used as surfactants to enhance bioavaialbility of poorly soluble drugs.

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E.g., Ethoxylated castor oil and ethoxylated hydrogenated castor oil.

- **Polyalcohol esters of edible fatty acids:** The alcohols may be polyglycerol, propylene glycol, sorbitan or mono-anhydro sorbital (span 80 and tween 80).

2.2. Surfactants

- The surfactants used in these formulations are known to improve the bioavailability by various mechanisms including improved drug dissolution, increased intestinal epithelial permeability, increased tight junction permeability and decreased / inhibited p-glycoprotein drug efflux.
- Non-ionic surfactants with a relatively high hydrophilic- lipophilic balance (HLB) were advocated for the design of self-dispersing systems, where the various liquid or solid ethoxylated polyglycolyzed glycerides and polyoxyethylene 20 oleate (Tween 80) are the most frequently used excipients.
- 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.
- The usual surfactant concentration in self-emulsifying formulations required to form and maintain an emulsion state in the GI tract ranged from 30 to 60% w/w of the formulation. A large quantity of surfactant may irritate the GI tract.
- The high HLB and subsequent hydrophilicity of surfactants is necessary for the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous environment, providing a good dispersing/self emulsifying performance.
- The surface-active agents are amphiphilic by nature, and they are therefore usually able to dissolve and even solubilize relatively high quantities of the hydrophobic drug. The latter is of prime importance for preventing precipitation within the GI lumen and for the prolonged existence of the drug molecules in soluble form, which is vital for effective absorption.
- The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of self-micro emulsifying formulations [5, 6].

2.3. Co-solvents

In order to produce an effective self-emulsifying system relatively high surfactant concentrations (usually more than 30% w/w) are needed. They can be organic or aqueous [6, 7].

- Organic solvents, mostly suitable for oral may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base. These solvents sometimes play the role of the co-surfactant in the micro emulsion systems.
  E.g., Ethanol, propylene glycol and polyethylene glycol.

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- Addition of an aqueous solvent such as triacetin/ glyceryl triacetate act as co-solvents. Triacetin is suitable since it is miscible in the oil lipid phases and it can be used to solubilize a hydrophobic drug.
  E.g., Glycerin.

2.4. Consistency builder

Additional material can be added to alter the consistency of the emulsions.

E.g., Tragacanth, cetyl alcohol, stearic acid and beeswax.

2.5. Polymers

Inert polymer matrix representing from 5 to 40% of composition relative to the weight, which is non-ionizable at physiological pH and being capable of forming matrix are used.

E.g., Hydroxypropyl methyl cellulose and ethyl cellulose.

3. Factors Affecting Self Emulsifying Drug Delivery Systems

3.1. Polarity of the Lipophillic 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 value, the chain length and degree of unsaturation of the fatty acid, 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. The highest release was obtained with the formulation that had oil phase with highest polarity [8].

3.2. Nature and Dose of the Drug: Drugs which are administered at very high dose are not suitable for SEDDS unless they have extremely good solubility in at least one of the preferably lipophillic phase. The drugs which have limited or less solubility in water and lipids are most difficult to deliver by SEDDS. The ability of SEDDS to maintain the drug in solubilised form is greatly influenced by the solubility of the drug in oil phase. If surfactant or co-surfactant is contributing to the greater extent in drug solubilisation then there could be a risk of precipitation, as dilution of SEDDS will lead to lowering of solvent capacity of the surfactant or co-surfactant. Equilibrium solubility measurements can be carried out to anticipate potential cases of precipitation in the gut. However, crystallisation could be slow in the solubilising and colloidal stabilizing environment of the gut [9].

4. Mechanism of Self Emulsification

Self-emulsification occurs when the entropy change that favours 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 required to create a new surface between the two phases,

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

Where,

G is the free energy associated with the process

N is the number of droplets of radius, r, and

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σ 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. 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. In the case of self-emulsifying systems, the free energy required to form the emulsion is either very low and positive, or negative. 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. Emulsification can be associated with the ease by which water penetrates into the various liquid crystals or phases get formed on the surface of the droplet. The addition of a binary mixture (oil/non-ionic surfactant) to the water results in the interface formation between the oil and aqueous continuous phases, followed by the solubilization of water within the oil phase owing to aqueous penetration through the interface, which occurs until the solubilization limit is reached close to the interface. Further, aqueous penetration will result in the formation of the dispersed liquid crystalline phase. As the aqueous penetration proceeds, eventually all materials close to the interface will be liquid crystal, the actual amount depending on the surfactant concentration in the binary mixture once formed, rapid penetration of water into the aqueous cores, aided by the gentle agitation of the self-emulsification process causes interface disruption and droplet formation. The high solubility of these self-emulsified systems to coalescence is considered to be due to liquid crystal interface surrounding the oil droplets [9, 10].

5. Characterization of SEDDS

5.1. Ternary phase diagram

Pseudo ternary phase diagrams are often constructed for the development of SEDDS that help in determining the optimum concentrations of different excipients required to obtain homogenous pre-concentrates, self emulsification ability and drug loading. Each corner of pseudo ternary diagram represents 100% of a particular component and when more than three components are used, closely related ones are grouped together as one component and treated as such in the diagram. They are generally generated by water titration method, where, water is incorporated to the SMEDDS pre-concentrate in drop wise manner, with gentle stirring to allow equilibration. Addition of water leads to formation of complex systems ranging from gels to systems containing lamellar, hexagonal or cubic faces to micro-emulsions. The mixture is usually examined for transparency. The points from clear to turbid and turbid to clear are designated as emulsion and micro-emulsion [11].

5.2. Visual assessment

Visual assessment provides important information about the self-emulsifying and micro emulsifying property of the mixture and about the resulting dispersion.

5.3. Turbidity measurement

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This is to identify efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time measurement. The measurements are carried out on turbidity meters like Hatch turbidity meter, Orbeco-Helle turbidity meter [12].

5.4. Droplet size

The size of the droplet in self-emulsification determines the rate and extent of drug release as well as the stability of the emulsion. Photon correlation spectroscopy, microscopic techniques or a Coulter Nano-sizer 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.

5.5. Zeta potential measurement

This is used to identify the charge of the droplets. In conventional SEDDS, the charge on an oil droplet is negative due to the presence of free fatty acids. However, incorporation of a cationic lipid, such as Oleylamine at a concentration range of 1-3% will yield cationic SMEDDS. Zeta potential helps to predict the stability flocculation effect in emulsion systems. If zeta potential falls below a certain level, colloid will aggregate due to attractive forces. Conversely, a high zeta potential maintains a stable system [11, 12].

5.6. Determination of emulsification time

The rate of self emulsification is usually determined by adding a dose of the SEDDS pre-concentrate, preferably in a capsule, to a relevant amount of water or bio relevant media. Rate of dispersion is usually determined by visual observation or by monitoring the change of turbidity of dispersion using a UV spectrophotometer or nephelometer.

5.7. Cryo- Transmission Electron Microscopy (TEM) studies

These studies are carried out in a controlled environment confirmation system, where thin liquid film is obtained on the grid, by placing small amount of sample on a carbon paper, which is supported by a filter paper. Thereafter this grid is quenched in liquid ethane at -180 ^{0}C and transferred to liquid nitrogen at -196 ^{0}C. Then the samples were characterized with a TEM microscope [13].

5.8. Liquefaction time

This test estimates the time required to melt solid SEDDS in *in-vivo* studies in the absence of agitation to replicated GI conditions.

E.g., Tablet is enclosed in a transparent polyethylene film and tied to the bulb of a thermometer with a thread. And then it is placed in a round bottom flask containing 250 mL of simulated gastric fluid without pepsin maintained at 37 ± 180 ^{0}C. The time taken for liquefaction is subsequently noted [14].

5.9. Electron microscopic studies

Freeze-fracture electron microscopy has been used to study surface characteristics of such dispersed systems. Particle size analysis and low-frequency dielectric spectroscopy have been used to examine the self-emulsifying properties of a mixture of mono- and diglycerides of capric and caprylic acids, and tween 80 systems [13, 14, & 15].

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5.10. Small angle neutron scattering

Small-angle neutron scattering can be used to obtain information on the size and shape of the droplets. This study uses the interference effect of wavelengths scattered from different materials in a sample (different scattering-length densities).

5.11. Small-angle X-ray scattering

This small-angle scattering technique gives the information about shape and size of macromolecules, characteristic distances of partially ordered materials, pore sizes and other data. By this technique we get structural information of macromolecules between 5 and 25 nm, of repeat distances in partially ordered systems of up to 150 nm.

6. Evaluation of SEDDS

6.1. Thermodynamic stability studies
6.2. Dispersibility test
6.3. Turbidimetric evaluation
6.4. Viscosity determination
6.5. Droplet size analysis particle size measurement
6.6. Refractive index and percent transmittance
6.7. Electroconductivity study
6.8.*In-vitro* diffusion study
6.9. Drug content

6.1.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 capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug [15].

6.1.1. Heating cooling cycle: Six cycles between refrigerator temperature 4^0C and 45^0C with storage at each temperature of not less than 48hr is studied. Formulations which are stable at these temperatures are subjected to centrifugation test.

6.1.2. Centrifugation: Passed formulations are centrifuged thaw cycles between -21^0C and $+25^0$C with storage at each temperature for not less than 48hr at 3500 rpm for 30 min. The formulations that does not show any phase separation are taken for the freeze thaw stress test.

6.1.3. Freeze thaw cycle: Three freeze thaw cycles between - 21 ^{0}C and +25 ^{0}C with storage at each temperature for not less than 48hr was done and the

formulations that have passed this test showed good stability with no phase separation, creaming, or cracking.

6.2. Dispersibility test

The efficiency of self-emulsification of oral emulsion is assessed using a standard USP XXII dissolution apparatus 2. One millilitre of each formulation was added to 500 mL of water at 37 ± 0.5 ^{0}C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation [16].

The *in-vitro* performance of the formulations is visually assessed using the following grading system:

Grade A: Rapidly forming (within 1 min), 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, greyish 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.

6.3.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 HCl) under continuous stirring (50 rpm) on magnetic plate at ambient temperature, and the increase in turbidity is measured using a turbidimeter [15, 16].

6.4. Viscosity determination

Since the self emulsifying drug delivery system is generally administered in soft gelatin or hard gelatin capsules, it can be easily pourable into capsules and such system should not be too thick to create a problem. The rheological properties of the micro emulsion are evaluated by Brookfield viscometer.

6.5. Droplet size analysis Particle size measurement

The droplet size of the emulsions is determined by photon correlation spectroscopy using a Zeta sizer that is 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 nano-metric size range of the particle is retained even after 100 times dilution with water which proves the system's compatibility with excess water [17].

6.6. Refractive index and percent transmittance

Refractive index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by refractometer by placing drop of solution on slide and compare with water (1.333). The percent transmittance of the system is measured at particular

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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 %, then formulation have transparent nature [16, 17].

6.7. Electroconductivity study

SEDDS contains ionic or non-ionic surfactant, oil, and water, which requires this test is used to measure the electoconductive nature of system. The electro conductivity of resultant system is measured by electoconductometer.

6.8. *In-vitro* diffusion study

In-vitro diffusion studies are performed to study the release behaviour of formulation from liquid crystalline phase around the droplet using dialysis technique. One end of cellulose dialysis tubing (7cm in length) was tied with thread, and then 1mL self emulsifying formulation was placed in it along with 0.5mL of dialysing medium (pH 6.8 phosphate buffer). The other end of the tubing was also secured with thread and allowed to rotate freely in 200 mL of dialysing medium and stirred continuously at 100 rpm with magnetic bead on magnetic plate at 37^0C. Aliquots of 1mL were removed at different time intervals and diluted further. Volumes of aliquots were replaced with fresh dialysing medium each time. These samples were analyzed quantitatively for drug dialyzed across the membrane at corresponding time by using UV-Visible Spectrophotometer [16, 17].

6.9. Drug content

Drug from pre-weighed 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.

7. Super Saturable Self Emulsifying Drug Delivery Systems (S-SEDDS)

The S-SEDDS approach is to generate a protracted (extended) supersaturated solution of the drug when the formulation is released from an appropriate dosage form into an aqueous medium. The high surfactant level typically present in SEDDS formulations can lead to GI side-effects and a new class of supersaturable formulations, including Supersaturable Self Emulsifying Drug Delivery Systems (S-SEDDS) formulations, have been designed and developed to reduce the surfactant side-effects and achieve rapid absorption of poorly soluble drugs. These are SEDDS formulations having reduced amount of surfactant, and a crystal growth inhibitor such as HPMC.

Reducing the amount of surfactant in a SEDDS in order to generate a supersaturated state on dilution of the formulation with an aqueous medium can result in rapid precipitation of the poorly soluble drug, incorporation of HPMC or other cellulosic polymeric excipients in the SEDDS formulations can sustain the supersaturated state by preventing precipitation of the drug.

The cellulosic polymers are excellent crystal growth inhibitors and are effective in prolonging the supersaturated state of the drugs in GIT. The ability to generate a supersaturate state with HPMC with the S-SEDDS may be due to the formation of widely spaced cellulosic-polymer network that is formed by the HPMC chains in water.

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HPMC chain may inhibit nucleation, as well as crystal growth by adsorption of the HPMC molecules onto the surface of the nuclei, or onto the surface of crystals. Surpersaturation is intended to increase the thermodynamic activity to the drug beyond its solubility limit and, therefore, to result in an increased driving force for transit into and across the biological barrier [18].

Various dosage forms of S-SEDDS are as listed below:

- Self-emulsifying sustained/controlled-release tablets
- Self-emulsifying sustained/controlled-release pellets
- Self-emulsifying solid dispersions
- Self-emulsifying beads
- Self-emulsifying sustained-release microspheres
- Self-emulsifying nanoparticles
- Self-emulsifying suppositories
- Self-emulsifying implants
- Dry emulsions.

8. Solid Self Emulsifying Drug Delivery Systems

SEDDS are generally encapsulated either in hard or soft gelatin capsules. Lipid formulations however may interact with the capsule resulting in either brittleness or softness of the shell. To address this limitation, liquid lipid formulations could be transformed into free flowing powder by loading the formulation on a suitable solid carrier. Liquid lipid loading onto solid carriers combines the features of a lipid based drug delivery system (enhanced solubility and bioavailability) and solid dosage form (low production cost, convenience of process control, high stability and reproducibility etc) [17, 18].

9. Solidification techniques for converting liquid/semisolid SEDDS to Solid-SEDDS

Solid SEDDS were mainly developed by adsorption of solid carriers, spray drying, melt extrusion, dry emulsion, solid dispersion etc. These solid- SEDDS can be converted into pellets, tablets and capsules [17, 18 & 19].

9.1. Spray Cooling
9.2. Spray Drying
9.3. Adsorption on Solid Carriers
9.4. Melt Granulation
9.5. Melt extrusion
9.6. Spheronization
9.7. Solid Lipid Nanoparticles

9.1. Spray Cooling

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The molten droplets are sprayed into cooling chamber, which will congeal and re-crystallize into spherical solid particles that fall to the bottom of the chamber and subsequently collected as fine powder. The fine powder may then be used for development of solid dosage forms tablets or direct filling into hard shell capsules. Many types of equipment are available to atomize the liquid mixture and to generate droplets: rotary, pressure, two-fluid or ultrasonic atomizers.

9.2. Spray drying

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 evaporates, and forming dry particles under controlled temperature and airflow conditions. Such particles can be further prepared into tablets or capsules.

9.3. Adsorption to solid carriers

The advantage of solid carriers is, they have the property to take up liquid/semisolid formulation as self emulsifying system. The adsorption process is simple and just involves addition of the liquid formulation onto carriers by mixing in a blender. The resultant powder may then be filled directly into capsule or alternatively, mixed with suitable excipients before compression into tablets. The major advantage of using this technique is good content uniformity. SEDDS can be adsorbed at higher levels (up to 70% w/w) onto suitable carriers. Solid carrier can be microporous substances, high surface area colloidal inorganic adsorbent substances, cross-linked polymers or nanoparticle adsorbent. [19]

E.g., Silica, silicates, magnesium trisilicate, magnesium hydroxide, talcum and crosspovidone.

9.4. 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. The melted binder forms liquid bridges with the powder particles that shapes into small agglomerates (granules) which can, be transform to spheronized pellets by further mixing. It is a one-step operation, melt granulation offers several advantages compared with conventional wet granulation, since the liquid addition and the subsequent drying phase are omitted. The main parameters that control the granulation process are impeller speed, mixing time, binder particle size, and the viscosity of the binder during melt granulation. Nucleation (onset of granule formation) is largely affected by binder viscosity at high impeller speed and binder particle size at low speed. Fine or atomized excipients with low viscosity at high impeller speed favour a homogenous "distribution" of the binder onto the surface of the powder. Immersion of the powder on the other hand is the preferred mechanism which is assisted by combination of large binder particles possessing high viscosity and mixing under low impeller speed. Generally, lipids with low HLB and high melting point are suitable for sustained release applications. Semi-solid excipients with high HLB on the other hand may serve in immediate release and bioavailability enhancement.

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The progressive melting of the binder allows the control of the process and the selection of the granule's size [18, 19].

Advantages:

- One step simplicity process
- Absence of solvents
- Potential for the highest drug loading capacity.

9.5. Melt Extrusion

Extrusion is a process of converting a raw material with plastic properties into a product of uniform shape and density by forcing it through a die under controlled temperature, product flow and pressure conditions. The size of the extrude aperture will determine the approximate size of the resulting spheroids (Pellets). Melt extrusion is a solvent free process that allows high drug loading as well as content uniformity for low dose high potency actives.

9.6. Extrusion Spheronization

The extrusion spheronization process is commonly used in the pharmaceutical industry to make uniformly sized pellets. This process requires the following steps:

- Mix dry active ingredients and excipients to form a homogeneous powder
- Wet massing with binder
- Extrusion into a spaghetti-like extrudate
- Spheronization from the extrudate to spheroids uniform size
- Drying
- Sifting to achieve the desired size distribution [18, 20].

9.7. Solid Lipid Nanoparticles

Solid Lipid Nanoparticles and Nanostructured Lipid Carriers are two types of submicron size particles (50– 1000 nm) composed of physiologically tolerated lipid components. SLN are produced by high-pressure homogenization of the solid matrix and drug with an aqueous solution of the glyceryl dibehenate as solid lipid matrix and poloxamers 188 or polysorbates 80 as surfactants. They typically contain a liquid excipient such as medium chain triglycerides in addition to classic components of SLN. They have been mainly used for controlled-release applications in oral, intravenous or topical route [17, 19].

10. Applications of SEDDS

The applications of SEDDS are shown in **Table 1** [19, 20].

Table 1. Applications of SEDDS

DRUG	SURFACTANT	OIL	CO-SOLVENT	RESULT
Ketoprofen	Captex 200	Tween 80	Capmul MCM	Increased bioavalability

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Atorvastatin	Labrafil, estol & isopropyl myristate	Cremophor EL, Cremophor RH40	Labrafil 1944	Oral bioavailability increases 1.55 times than conventional tablets
Carvedilol	Labrasol	Labrafil M 1944 CS	Transcutol P	Bioavailability increased upto413%
Simvastatin	Caproyl 90	Cremophor EL	Carbitol	Oral bioavailability is 1.5 times higher than conventional tablets
Itraconazole	Tocopherolacetate	PluronicL64	Transcutol	Oral bioavailability increased without influence of food
CoenzymQ10	Captex 200	Labrasol	Lauroglycerol	Oral bioavailability increased upto 2 folds than powder formulaton
Diclofenac sodium (SE Tablet)	Goat fat	Tween 65		Better release rate

11. CONLUSION

Self-emulsifying drug delivery systems are a hopeful approach for the formulation of lipophilic drugs. With future developments in this novel technology, SEDDS will remove deficiencies associated with delivery of poorly soluble drugs. Thus, this field requires further exploration and research to bring out a wide range of commercially available self-emulsifying formulations. Even though it is an effective technique, here also some disadvantages are there, like lack of good predicative in vitro models for assessment of the formulations, and higher concentrations of surfactant to be used may causes some allergic reactions. Further development will be based on *in-vitro* - *in-vivo* correlations and therefore different prototype lipid based formulations needs to be developed and tested using *in- vivo* and *in-vitro* methods.

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To conclude, we can say that this system is not only about lipids and surfactants but associated with delivery of poorly soluble drugs.

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