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Solid Self Emulsifying Drug Delivery System: A Novel Approach in Solubility and Bioavailability Enhancement of Poorly Soluble Drugs

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Abstract: Low aqueous solubility and oral bioavailability is a main concern for the formulation research scientist in the field of modern drug delivery system. In recent years much more attention has been focused on the development of self-emulsifying drug delivery system which is one of the most promising approaches to improve the bioavailability of hydrophobic drugs. The SEDDS is isotropic mixture of drug, oil, surfactants, co surfactants form emulsion on mixing with water with energy. This conventional SEDDS prepared in the form of liquid and semisolid which can offer some demerits. So Solid self-emulsifying drug delivery system (S-SEDDS) which is formulated by solidification of liquid and semisolid self-emulsifying ingredients into various solid dosage form such as powders, tablet, capsule, solid dispersion etc. by various methods such as melt granulation, melt extrusion, spray drying, adsorption to solid carriers. The review presents in this article provides an updated knowledge of the recent trends in S-SEDDS with related to the selection of the ingredients, dosage form developments, solidification methods associated with problems and their remedies, evaluation and their application. Finally, the present problems and the possible future investigation in this field is pointed out in this review article.

***Key Words*:** Solid self-emulsifying drug delivery system, BCS class, Melt granulation, Dry emulsion, Bioavailability

Introduction:

In recent years various surveys on drug discovery shows that 40 % of new drug entity shows low solubility in water, which may leads to poor oral bioavailability. So it is a great challenge to pharmaceutical scientist to transform these molecules into orally administered dosage forms with improved bioavailability. There are number of methods to overcome the low solubility, low dissolution and low bioavailability problems which May results into increased therapeutic efficacy of low solubility drugs. The methods like complex formation with cyclodextrins, salt formation, solid dispersion, liposome formation, co precipitation, micro ionization. But one of the prominent and commercially available formulation approaches to solve these problems is self-emulsifying drug delivery system.

Self-emulsifying drug delivery system are defined as isotropic mixture of drug, oil or lipid, surfactants and co-surfactants that quickly forms a fine oil in water (O/W) emulsion or lipid globules, ranging in size from approximately 100 nm for SEDDS & less than 50 nm for self-micro emulsifying drug delivery system (SMEDDS), when exposed to physiological fluid. But traditional formulation of SEDDS involves dissolution of drugs into oils and then their blending with suitable solubilizing materials. However, SE preparation are normally formulated as liquids that produces some drawbacks such as high production cost, low stability, low drug loading and less choices of dosage forms. More importantly, the greater concentration (30-60%) of surfactants in the preparation can cause gastrointestinal (GI) irritation.

To overcome these drawbacks, solid self-emulsifying drug delivery system (S-SEDDS) have been extensively reported in recent years as alternative approach to SEDDS. A number of solidification methods such as adsorption to solid carriers, spray drying, melt granulation, melt extrusion or extrusion spheronization and nanoparticle technology have been used for the preparation of SSEDDS. In 1990's SSEDDS were usually formulated in the form of self-emulsifying capsules, self-emulsifying solid dispersion and dry emulsion, but other solid self-emulsifying dosage forms have been emerged in recent years, such as self-emulsifying tablet, pellets, beads, sustained release microspheres,, nanoparticle, suppositories and implants. [1-22]

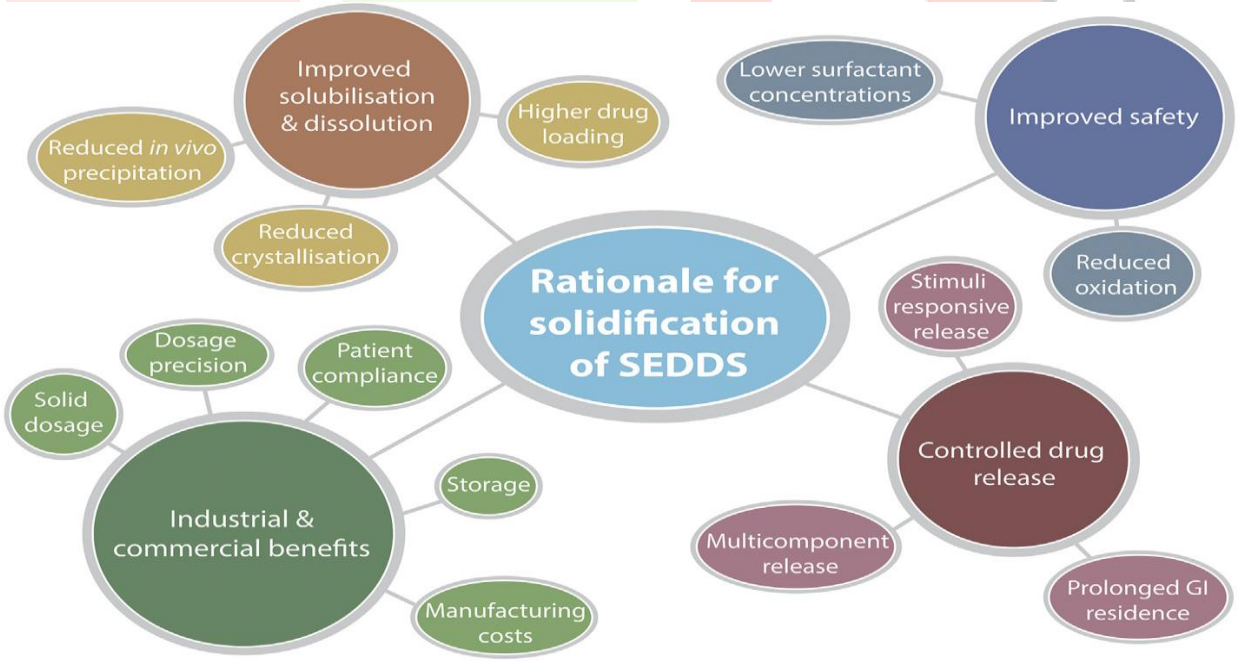

Fig.1. Approaches for converting liquid-SEDDS into solid dosage form [7]

Advantages:

1) Improvement in solubility and dissolution of poorly soluble (BCS Class II) drugs. [11]
2) Improvement in oral bioavailability of BCS class II and IV drugs.
3) Ease of manufacturing and scale up. [19]
4) Provides quick onset of action.
5) Improved drug loading capacity.
6) Improved stability of drugs.
7) Better patient compliance.
8) Provide protection to the drugs.
9) Reduction in drug dose.
10) Decreases inter-subject intra-subject variability and food effects. [13]

Disadvantages:

1) Lack of good predicative in vitro models. [13]
2) Need of different prototype lipid based formulation. [15]
3) Chemical instabilities of drugs due to high concentration of surfactants in formulation (30-60%). [19]

COMPOSITION OF SSEDDS:

1. **Active Pharmaceutical ingredient:**

SSEDDS are used to improve the solubility of poorly water soluble drug candidates. In SSEDDS formulations mostly BCS class II drugs preferred, such as glibenclamide, ezetimibe, nepafeanc aceclofenac, eprosartan, nifedipine, itraconazole, griseofulvin, repaglinide, rosuvastatin, carvedilol, telmisartan, clonazepam etc. [13-21]

2. **Excipients:**

In SSEDDS self-emulsification process is totally depends on concentration of oil and surfactants ratio, surfactants/ co-surfactants ratio and temperature at which actual self-emulsification process occurs. So these entire factors which influences on SE process must be taken into consideration during selection of excipients in SSEDDS. The drug must be physically and chemically stable with preparations of SSEDDS and drug release pattern must be constants during the shelf-life of formulations. The main excipients in solid self-emulsifying system include oils, surfactants/co-surfactants and co-solvents. [21]

a. **Oil:** The oil plays a vital role in the drug bioavailability and lymphatic transportation, thereby increasing absorption from GI tract based on the molecular nature of the triglycerides. [13] Oil can solubilizes the necessary dose of the lipophilic drug and enable the self-emulsification process. In the formulation of SSEDDS both long chain and medium chain triglyceride oil with non-identical degree of saturation. Commonly known saturated oil include lauric, myristic and capric acid; while unsaturated fatty acids are oleic acid, linoleic acid, and linolenic acid. [19-39]

Table 1: Types of oil used in marketed SSEDDS

Sr. No.	Marketed Formulations	Drug	Oils used
1	Accutane soft gelatin capsule	Isotretinoin	Hydrogenated soya bean oil
2	Marinol soft gelatin capsule	Dronabinol	Sesame oil
3	Prometrium soft gelatin capsule	Progesterone	Peanut oil
4	Depakene capsule	Valproic acid	Corn oil

b. Surfactants:

In case of surfactants to form oil in water emulsion (O/W), surfactants with high hydrophilic lipophilic balance (HLB) must be preferred and it ensures the efficient self dispersibility and stability of the formed emulsion. Generally the concentration of surfactants to form a stable SSEDDS is 30-60%. It is necessary to measure the concentration of surfactants accurately because larger concentration may cause the GI irritation. Due to the high HLB and hydrophilicity so it can immediately forms oil I water droplets which will leads to rapid spreading of the formulation into aqueous medium, so by this way good emulsifying performance can be achieved. [9-13] Nature of the surfactants used in SSEDDS could be ionic, nonionic; here nonionic surfactants are mostly used in formulation due to its less toxicity as compared to ionic surfactants. Surfactants play a vital role in formulation by following mechanism,

- Increased intestinal epithelial permeability,
- Increased tight junction permeability.
- Improved drug dissolution, [21]

A list of surfactants used in various marketed preparation of SSEDDS are listed as follows, [37-39]

Table 2: Types of Surfactants used in marketed SSEDDS

Sr. No.	Marketed formulation	Drug	Surfactants used
1	BCNU self-emulsifying implant	Carmustine	Cremophor RH 40
2	Targretin hard gelatin Capsule	Bexarotene	Tween 20
3	Gengraf soft gelatin capsule	Cyclosporine	Span 80,Tween 80
4	Agenerase oral solution	Amprenavir	Poly ethylene Glycol
5	Agenerase soft Gelatin capsule,	Amprenavir	D-alpha Tocopheryl

c. Co-surfactants: Use of larger concentration of surfactants in formulation may leads to GI disturbances and GI irritation, so to avoid these it is necessary to lower down the surfactants concentration and this can be achieved by use of Co-surfactants. [21] Role of the surfactants and Co-surfactants in combination is to lower down the interfacial surface tension, So organic solvents like ethanol, poly ethylene glycol (PEG), and propylene glycol are able to dissolve larger amount of drug or hydrophilic surfactants into lipid base and it

is suitable for oral delivery due to this reason they can be used as a Co-surfactants in SSEDDS. Role of the surfactants in the formulation is as follows,

- The fluidity of the interface can be improved.
- Changing surfactant partitioning properties of system due to change in HLB value and spontaneous curvature of the interface.
- Prevents the formation of gelled micro emulsion. [9-10]

Table 3: Types of Co-surfactants used in marketed SSEDDS

Sr. No.	Marketed Formulations	Drug	Co-surfactants used
1	Gengraf hard gelatin capsule	Cyclosporine	Ethanol
2	Neoral soft gelatin,	Cyclosporine	Propylene glycol
3	Sandimmune soft gelatin capsule.	Cyclosporine	Glycerin

d. Co-solvents: Co solvents such as mono ethyl ether (transcutol), propylene glycol, polyoxyethylene, propylene carbonate, ethanol and glycerin may help in dissolving the immiscible phases of formulation (oil/aqueous). [9] Co-solvents are used to solubilize either hydrophilic surfactants or hydrophobic drugs in oil phase. Co-solvents may also refer as Co-surfactants based on their use in formulations. Some of the co-solvents used in various formulation of SEDDS and SSEDDS are as follows, [13]

- Ethanol
- Propylene glycol
- Poly ethylene glycol
- Glycerin [19]

e. Other Excipients used in SSEDDS:

1) Viscosity enhancer: Viscosity modifiers are used to improve the viscosity of the lipid based formulations of self-emulsifying drug delivery system (SEDDS) after that this lipid based formulation will be converted into solid self-emulsifying drug delivery system. Some commonly used examples of viscosity modifiers are listed as follows,

- Acetyl alcohol
- Bees wax
- Stearic acid
- Tragacanth [13]

2) **Consistency binder:** Consistency binders used in formulation to improve the emulsion and stability of micro emulsion structure after the administration of solid self-emulsifying dosage forms. Example of the consistency binder are listed as follows
   - Cetyl alcohol
   - Tragacanth [13]

3) **Polymers:** Polymer which is inert in nature is used to improve the viscosity and consistency of the preparations. Polymers are used for various purposes in SSEDDS such as mucoadhesion, sustained release formulation of drug, in situ gelling system and as a permeation enhancer. Various polymers are used in SSEDDS are as follows,
   - Carbopol 934
   - Chitosan
   - Hydroxy propyl methyl cellulose
   - Poly carbonate
   - Ethyl cellulose [13]

Mechanism of Self Emulsification:

Mechanism of self-emulsification has been suggested by Reiss, states that self-emulsification process occurs when entropy change favoring dispersion is higher than energy required to increase the surface area of dispersion, i.e. self-emulsification occurs when entropy or energy change occurs. The free flow energy of the conventional emulsion preparation is direct function of the energy required to forms a new surface between the oil and water phases and it can be explained by following equation, [3-21]

$$\Delta G = \Sigma N \pi r 2 \sigma \quad \ldots\ldots\ldots\ldots\ldots\ldots \text{(I)}$$

Where,

ΔG is free energy associated with process,

N is the droplet numbers,

r is radius of globules,

σ is the interfacial energy.

The oil and water phases of emulsion tends to separate with time to reduce the interfacial areas and the free energy of the system, so conventional emulsifying agents stabilize emulsion resulting from aqueous dilution by forming a monolayer around the emulsion globules, by forming a barriers to coalescence and through reducing interfacial energy. Self- emulsification occurs with self-emulsifying formulations because the free energy required to form an emulsion is low or positive / negative. [37-39]

Method of Preparations:

Solidification techniques for converting liquid SEDDS into SSEDDS: Various techniques are available to convert the liquid or semisolid SEDDS into SSEDDS they are as follows,

1. **Melt granulation:** Melt granulation is a technique in which powder agglomeration is obtained by the mixing of binders that melts at low temperatures. Melt granulation also referred as thermoplastic Palletization or one step techniques and it provides a large number of merits over a conventional wet granulation. Various types of semisolid liquid and solid are used as melt able binders. To formulate a good quality of binders with melt granulation process it is necessary to control various parameters such as impeller speed, mixing time, viscosity of the binders and particle size of the binders. [1-3]

2. **Melt Extrusion:** Melt extrusion is a solvent free process for converting SEDDS into SSEDDS, with high drug loading capacity about 60% and content uniformity. Extrusion is a method of transforming a raw material with plastic properties into a formulation of uniform shape and density by passing it through a die under controlled temperature, pressure condition and well maintained product flow. [1-13]
3. **Spray Drying:** Spray drying is simple techniques for converting liquid SEDDS into SSEDDS. In this method liquid SEDDS is mixed with the solution of solid carriers with continuous stirring to produce o/w emulsion. This resultant solution is atomized into drying chambers so by this way volatile phase of the formulation evaporates, it will leads to formation of dry particles under a controlled temperature and airflow conditions. The dried particle are collected from chamber and further processed for compression to form a tablet, capsules and pellets. The design of dried chamber, atomizer, temperature pattern and airflow pattern are selected according to characteristics of products and specification of powders. [1-21]
4. **Adsorption to solid carriers:**

   Adsorption to solid carriers is widely used method to transforming liquid SEDDS into SSEDDS. In this method the free flowing powders may be obtained from liquid SE formulations, this methods involves the mixing of liquid SE formulations onto solid carriers by mixing in blender. Then resultant powder is directly filled into capsules or further mixed with other excipients before compression into tablets.

   Solid carriers can be cross linked polymers, high surface area colloidal inorganic adsorbent materials or nanoparticle adsorbents, for examples, silicates, silica, talcum, magnesium trisilicate, magnesium hydroxide, cross-linked sodium carboxymethy cellulose, cross-linked polymethyl methacrylate and crospovidone, this cross-linked polymers can creates suitable conditions to sustain drug dissolution and also helps in slow down of drug reprecipitation. Also various nanoparticle adsorbents such as porous silicon dioxide, carbon nanotubes, carbon nanohorns, fullerene and charcoal are used as solid adsorbents in formulation of SSEDDS. [16-21]
5. **Extrusion spheronization:** In pharmaceutical industry extrusion spheronization method is used to make uniform sized pellets. Extrusion spheronization methods involves the following steps,
   - **a.** Mix all the dry active ingredients and excipients to form a homogeneous powder blends.
   - **b.** Wet massing with binders.
   - **c.** This above formed mixture placed in extrusion like spaghetti-like extrudate.
   - **d.** Followed by spheronization from the extrudate to spheroids uniform size and drying.
   - **e.** Then this mixture is shifted to achieve desired size distribution. [3-16]
6. **Capsule filling with liquid or semi-solid self-emulsifying formulations:**

   Capsule filling or microencapsulation is one of the simplest and most widely used methods for transforming liquid or semi-solid self-emulsifying formulation into solid self-emulsifying formulations (SSEDDS). [13]

   For liquid formulations it is two-step process:

   1. Filling of liquid formulations into empty capsule shells.
   2. Then sealing of the cap and body of the capsule by micro spray sealing and banding methods.

   For semi-solid formulations it is four step process:

   1. Heat all the semi-solid excipients at 20^0C or above its melting points.
   2. With continuous stirring incorporate active ingredients with above heated excipients.
   3. Then fill the capsule shell with molten mixture.
   4. Then cool it at room temperature.

Problems Associated To Solidification Methods:

There are various problems related to solidification methods they are as follows,

1. Absorption of the drug may affect due to nature of the excipients.
2. Drug release pattern may be affected due to concentration or amount of the solidifying excipients.
3. There are the chances of drug degradation during solidification methods.
4. Difficulty in securing content uniformity.
5. Solvents used in granulation may effects on formulations
6. In spray drying methods there is the chances of clogging of spray nozzle due to oil content.
7. Reduction in drug loading capacity. [1]

Remedies to Overcome the Problems Associated With Solidification Methods:

- Problems associated with absorption of the drugs overcome by, i) addition of sodium dodecyl sulfate into SE formulations. ii) Also the supersaturatable SEDDS was designed by using small quantity of HPMC and other polymers into formulations to prevent the precipitation of the drug by generating and maintaining a supersaturable state *in vivo*.
- Problems associated with release pattern of drug may be overcome by developing a gelled SEDDS. Colloidal silicon dioxide (Aerosiil 200) is used as gelling agents in oil-based system to reduce concentration or amount of required solidifying excipients and slow down the drug release. [1]

Dosage form development for Solid Self Emulsifying Drug Delivery System:

1) Dry emulsion: Dry emulsions are the powder dosage form which forms an emulsion when exposed to an aqueous solution by in vivo. This dry emulsion are typically prepared from oil/water (O/W) emulsion which containing a solid carrier such as lactose, maltodextrin in the aqueous phase by rotary evaporation, spray drying, freeze- drying. Spray drying method is one of the most frequently used for the preparation of dry emulsion. Spray drying techniques is used to remove the aqueous phase from O/W emulsion. In recent years one of the most exciting finding in this field is newly developed enteric coated dry emulsion formulations which is used for the oral delivery of proteins and peptide drugs. Dry emulsion can be further used for the formulation of tablets and capsule. Before the use this dry powder may be re-dispersed into water. Dry emulsion are powders that undergoes self- emulsification in vivo or when comes in contact with aqueous phase. [17]

2) Self-Emulsifying Capsules: Self emulsifying capsule is the capsule filled with the liquid, solid or semi-solid ingredients. After the oral administration the capsule readily dispersed in the gastro intestinal tract (GIT) to self-emulsifying system uniformly in the fluid to micron size to reach site of absorption. This self-emulsifying system contains small amount of a surfactant thereby it reduces the side effects associated with GIT. To improve the patient compliance, portability and to increase the stability of dosage forms mainly solid self-emulsifying capsules systems generally used in the market. In self-emulsifying capsule formulation if irreversible phase separation of micro emulsion occurs an improvement of drugs absorption cannot be expected. So to solve this problem, sodium dodecyl sulfate was added into the self-emulsifying formulations. [18-20]

3) Self-Emulsifying Tablets: Various combinations of oils and surfactants are used to prepare self-emulsifying tablets. It consists of solidified liquid self-emulsifying system either compressed into tablets. The SE tablets maintain a higher drug concentration in blood plasma over the same time frame as compared to the non-emulsifying tablets. Due to the restriction related to capsule volume and production equipment's which is needed for capsulation tablets are one of the most widely acceptable conventional solid dosage forms are the better choice to deliver the higher quantity of drug with additional excipients are essential to obtain compressible mixture for tableting to achieve suitable dissolution profile. Generally self-emulsifying sustained release and controlled release tablets was formulated. Now a days one of the newest research inn field of SE tablet is the SE osmotic pump tablet for this elementary osmotic pump system was chosen as the carrier system of SES. This osmotic pump system provides greater features such as stable plasma concentration, controlled drug release rate and improved bioavailability. [6, 15, 20]

4) Self-Emulsifying Solid dispersion: Solid dispersion is used to increase the rate of dissolution and also to improve the oral bioavailability of drugs that are poorly soluble in water and other aqueous solvents. Self-emulsifying solid dispersion is commonly prepared by hot melt granulation method. This self-emulsifying solid dispersion mass may be filled in capsule in the molten form. [13]

5) Self-Emulsifying Beads: Self-emulsifying beads are used to transform self-emulsifying system into a solid form with less amount of solidifying ingredients. In various investigations on SES it was investigated that loading SES into the micro channels of porous polystyrene beads prepared by using solvent evaporation method. [6, 17]

6) Self-Emulsifying Implants: Now days in research self-emulsifying have shown in advancement in solid self-emulsifying drug delivery system. Various co-polymers with hydrophilic region and 2 functional groups that can be cross linked are used to formulate self-emulsifying implants. These co-polymers are used as sealants. Self-emulsifying implants can deliver the drug in controlled manner. Various co-polymers based self-emulsifying implants had been incorporated as a grafting agent by molding methods. Drug like anti-cancer agents can be delivering through implants. By using this implants as a new invention drug delivery is possible up to 1 week. [8, 14]

7) Self-emulsifying Nanoparticle: In this formulation firstly prepare a molten mass of lipid and surfactants in which active drug was melted, and this mixture was injected drop wise into a tittered non-solvent. Then resultant self-emulsifying nanoparticle was separated using filtration method and dried at temperature which is less than their individual excipients melting points. Solvent injection method can be useful in the formulation of self-emulsifying nanoparticles. A second technique is called as sonication emulsion-diffusion-evaporation. [13, 14]

8) Self-Emulsifying Suppositories: In various studies investigators proved that solid self-emulsifying drug delivery system which can improves the gastrointestinal absorption also with have properties to increase rectal and vaginal absorption. For example Glycyrrhizin shows better therapeutic value in chronic hepatic disease when administered as self-emulsifying suppositories by vaginal and rectal route. [8, 14, 17]

9) Self-Emulsifying Sustained release microspheres: Self-emulsifying sustained release microspheres were prepared in various studies using the quasi-emulsion-solvent-diffusion method of the spherical crystallization techniques. Sustained release microspheres shown increased bioavailability of poorly soluble drug as compared to conventional liquid self-emulsifying drug delivery system. [6, 17-18]

10) Self-Emulsifying sustained release pellets: Pellets provides lots of advantages such as manufacturing flexibility, reducing intra and inter subject variability of plasma profiles and reducing GI irritation without lowering drug bioavailability. Pellets are prepared by using extrusion spheronization method. Sustained release pellets can release the drug by controlled release mechanism. Formulation of SE controlled release pellets by incorporating the drug candidate into self-emulsifying system which may increases their rate of release, whereas another coating of pellets with water soluble polymers can reduces the rate of drug release but simultaneously it also control the drug release. [10-20]

Evaluation and Characterization of Solid self-emulsifying drug delivery system:

1) Micromeritic properties of S-SEDDS: Prepared formulation of solid self-emulsifying drug delivery system evaluated for micromeritic properties such as bulk density, tapped density, Hausner's ratio, angle of repose, compressibility index. [23-31]

a. Bulk density: Bulk density is the mass of the powders divided by the total volume they occupy. Bulk density is also called as apparent or volumetric density. Bulk density were calculated using the following formula,

Bulk density = Mass of powder/ Volume of powder

b. Tapped density: Tapped density is the mass of powders divided by tapped volume of powders. It is determined by using following formula,

Tapped density = Mass of powder / Tapped volume of powder

Compressibility index: The compressibility index of prepared solid self-emulsifying formulation were determined by following formula,

Carr's compressibility index (%) = Tapped density- Bulk density / Tapped density X 100

c. **Hausner's ratio:** The Hausner's ratio can be determined by the following formula,

Hausner's ratio = Tapped density / Bulk density

d. **Angle of repose:** Angle of repose of S-SEDDS was determined by the simple funnel method. The diameter of the powder cone was measured and angle of repose calculated with the help of following equations,

$$\tan \theta = h / r \qquad \text{..... (II)}$$

Where,

θ = angle of repose

h = height of the pile

r = average radius of the power cone

2) **Drug content:** The percentage drug content of the formulation was estimated by dissolving the appropriate quantity of the solid self-emulsifying drug delivery system into suitable solvents. Then proper dilution of the samples were made and sonicated using the ultrasonicator for 15 to 30 minutes then this solution analyzed using double beam ultraviolet- visible spectrophotometer. [23-27]

3) **Droplet size analysis:** The resultant formulation of solid self-emulsifying drug delivery system was diluted with 100 ml of distilled water. Then the droplet size distribution and polydispersibility index of the formed micro emulsion were determined by using particle size analyzer such as Malvern Zetasizer 3000HS. [24-26]

4) **Fourier transform infrared spectroscopy:** Resultant formulation of solid self-emulsifying drug delivery system were mixed with little quantity of IR grade potassium bromide and then scanned in the appropriate range at 4000-400cm-1. IR and FTIR study is carried out to check the drug and drug excipients compatibility. Then after IR / FTIR determination obtained spectrum is compared with reported literature. [23-26]

5) **Scanning electron microscopy:** The surface morphological characters of the formulation and pure drug sample are determined by using scanning electron microscopy i.e. analytical electron microscope. To carry out this determination the sample is lightly sprayed on the double adhesive tape stuck on aluminum stub. Then this stub coated with the platinum to the thickness of above $10A^0$under an argon atmosphere by using Gold sputter module under high vacuum evaporator and then finally the stub containing coated sample is placed in the scanning electron microscope. [24-25]

6) **X-ray Diffraction:** X-ray diffraction study is carried out to analyze the diffraction patterns in drug before and after formulation. The physical state of the pure drug sample and its formulation of solid self-emulsifying drug delivery system is characterized by using x ray powder scattering (XRD) measurements with the help of X ray diffractometer. To carry out this study sample is tightly packed in the cavity of the aluminium sample holder by using a glass slide and measurements is performed at room temperature using monochromatic CuKα radiation at 35mA and at 40 kV over a 2θ range of 5^0 to 40^0 with a continuous scanning speed of 10^0 /minute. [27]

7) **Differential scanning calorimetry:** DSC thermo-gram is obtained for characterization of the pure drug sample and solid self-emulsifying drug delivery system. DSC is carried out to check the compatibility of the drug candidate with other material. DSC characterizes the sample using DSC instruments. To carry out this study the thermal traces of sample is obtained by heating the sample from 0-300ºC at heating rate of 10^0 C/min. Finally the thermo-grams, transition range, the onset of peak transition are recorded. [26]

8) ***In-Vitro* Dissolution Testing:** The dissolution study of solid self-emulsifying drug delivery system is performed using USP Apparatus I with basket and USP Apparatus type II with paddle at 75 rpm maintained at 37 ± 0.5^0C in 900 ml of dissolution medium. To maintain the physiological conditions number of different pH buffer solutions is used. Then aliquots of 5 ml were withdrawn at time intervals of 15 min, suitably diluted with solvents and analyzed by using spectrophotometrically at standard Y max nm range. [25-31]

9) **Emulsification Studies:** Emulsification studies were performed to evaluate the ability of the surfactants and co-surfactants to emulsify the oil phase. [24-26]

10) **Stability study:** Thermodynamic stability study of the formulation is carried out to observe the ability of the formulation to withstand different stress conditions according to ICH at different temperature. The prepared tablet dosage form of solid self-emulsifying drug delivery system subjected to stability study at different conditions of temperature and relative humidity. Then this sample is analyzed over a period of 3 to 6 months. Also formulation of solid self-emulsifying drug delivery system is evaluated for clarity of formed emulsion, emulsification time. [24-27]

11) **Zeta potential determination:** Zeta potential determination of the selected solid self-emulsifying drug delivery system containing formulations is carried out using Zetasizer instruments. Zeta potential is used to identify the charge on emulsion droplets also to gives an identification of the potential stability of the colloidal system of the formulations. [23-26]

12) **Disintegration test:** Solid SEDDS formulations which containing the active pharmaceutical ingredients of appropriate quantity were compressed into tablets or filled into hard gelatin capsule, then the test is carried out as per USP. The apparatus is operated till the tablet disintegrates and the time required for disintegration is noted. [26]

APPLICATIONS OF SOLID SELF-EMULSIFYING DRUG DELIVERY SYSTEMS:

A) Improved Bioavailability and Solubility

Oral bioavailability of a chemically stable drug is restricted by solubility and permeability of drug. Poor absorption of drug can be caused due to inadequate rate and extent of drug dissolution or due to the low permeability of drugs. So depends on solubility and permeability characteristics biopharmaceutical classification system (BCS) classify in to four classes i.e. Class I to Class IV. [2-21]

Bioavailability of BCS class II drugs is totally depends on their aqueous solubility and dissolution rate. For achieving better solubility and dissolution rate of this BCS class II drugs various techniques is available like micro ionization co solvent formation, micellar solubilization, solid dispersion and complexation, chemical modification, pH adjustment and self-emulsifying drug delivery systems. But in self-emulsifying drug delivery systems a fine particulate oil-in-water (o/w) emulsion improves the absorption of drugs. Therefore it leads to increasing in AUC, i.e. bioavailability and C_{max} is observed with various drugs. Some examples of drugs include Indomethacin, itraconazole, atorvastatin, amprenavir, carvedilol etc. [47-57]

B) Supersaturable SSEDDS

Supersaturable solid self-emulsifying drug delivery systems are developed to decrease the side effects related to high concentration of surfactants and Co-surfactants. As compared to the conventional self-emulsifying drug delivery systems solid self-emulsifying drug delivery systems significantly achieve the better toxicity and safety profile by reducing the concentration of surfactants and Co-surfactants used in formulations. [18-21]

C) In delivery of peptides

SEDDS and SSEDDS most commonly used for the delivery of macromolecules, which may include hormones, enzyme substrate, peptides and some other inhibitors because they protect macromolecules from enzymatic degradation. SSEDDS reduces the degradation of macromolecules and improves the absorption of drugs which ay leads to increased bioavailability of drugs. [18-21]

D) Drug targeting:

Now a days drug targeting is the ultimate aim of the formulation scientist. So to achieve this aim with improved efficiency and lower side effects, engineering of the pharmacokinetics and bio distribution of the drug candidate is necessary. This SSEDDS is important in therapeutics and plays a vital role in treatments of some chronic disease such as cancer.

1. Developing systems that increase the solubility and bioavailability of hydrophobic drug.
2. Minimizing the drug toxicity.
3. Increasing specificity.
4. Targeting the drug to specific cells or issues. [14, 18]

CONCLUSION AND FUTURE ASPECTS:

Solid self-emulsifying drug delivery systems are a novel promising approach for the formulation of drug candidates with poor aqueous solubility. Now a days several formulations have been developed to produce newly emulsified formulations as alternative approach to the conventional self-emulsifying drug delivery systems. Nearly 40% of drug candidates are hydrophobic and the oral delivery of this hydrophobic drug can be made possible by a novel approach of SSEDDS, which may leads to improved oral bioavailability and aqueous solubility of drugs.

Research has been shown that the oral absorption of BCS class II and class IV drugs is increased by converting or formulating it into SSEDDS. Firstly liquid or semisolid SEDDS is converted into SSEDDS containing tablets, capsule, pellets and powders etc. Various techniques are available to convert this SEDDS into SSEDDS such as melt granulation, extrusion and spheronization, spray drying and spray cooling, adsorption to solid carriers and lyophilization. Thus this field requires further exploration and research to bring out a wide range of commercially available self-emulsifying formulations. Selection of the excipients is main goal or task for developing the SSEDDS and all this aspects should represents main future working directions for the developments of SSEDDS.

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