CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: http://www.iajps.com *Review Article*

REVIEW ON SELF-EMULSIFYING DRUG DELIVERY SYSTEMS (SEDDs)

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Article Received: February 2022 **Accepted:** February 2022 **Published:** March 2022

Abstract

Self-emulsifying drug delivery systems (SEDDS) have been mainly investigated to enhance the oral bioavailability of drugs belonging to class II of the Biopharmaceutics Classification System. However, in the past few years, they have shown promising outcomes in the oral delivery of various types of therapeutic agents. In the early 1990s, solid lipid nanoparticles/ micro particles have been used as a drug carrier system and for sustaining the release of incorporated drugs. The SLN/SLMs are known to be solid at room temperature and they are classified within the submicron size range (50 – 1000 nm), hence incorporated drugs had a lower mobility than in the liquid oil. These microparticles have the potential to act as drug carrier systems, and as polymers. Their properties include physiologically compatibility, physiochemically stability and large-scale production. In microparticles/nanoparticles, preparation of the lipids used are very compactible and thus reduce toxicity. Solid lipid micro- or nano particles could be used in encapsulating lipophilic compounds. A suitable particle formulation could be used to achieve protein stabilization or a polymer mixture. Lipids, surfactants and water/ solvent are the major raw materials used in the preparation of micro/nanoparticles.

In the preparation of micro/nanoparticles different techniques used include: supercritical fluid method, high pressure homogenization, ultra-sonication/high speed homogenization, solvent evaporation method, solvent emulsification-diffusion method, microemulsion based method, spray drying method double emulsion method, precipitation technique and film-ultrasound dispersion.

***Keywords**: SEDDS, Microparticles, Microemulsion, Nanoparticles.*

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*Please cite this article in press **Ezegbe A. C** et al, **Review On Self-Emulsifying Drug Delivery Systems (SEDDs).**, Indo Am. J. P. Sci, 2022; 09(3)*

INTRODUCTION:

The high-pressure homogenization technique is the foremost technique and it has gained wide acceptability and reliability in the preparation of solid lipid micro / nano particles because it presents many advantages compared to the other techniques used in its preparation [1]. Some of the advantages include non-use of organic solvents, production time at a shorter interval, and faster scale up [2]. High pressure homogenization technique is sub-divided into hot homogenization and cold homogenization. A high temperature is normally applied in hot homogenization because higher temperatures result in lower particle sizes as a result of the decreased viscosity of the lipid phase [3]. Agarwal *et al* (2009) also reported that the hot homogenization technique involves a high shear device that is employed for a pre-emulsion production by mixing a hot aqueous surfactant solution with the drug loaded lipid melt [1]. The pre-emulsion is then placed once or several times in a pre heated high pressure homogenizer at a higher temperature above the lipid melting point. At room temperature, the formulations are then allowed to cool. The untoward effect of this method is that the degradation rate of the drug might be affected by high temperature especially thermolabile drugs [4]. For thermolabile and hydrophilic drugs, cold homogenization is the most suitable method. This is because during hot homogenization process, there would be partitioning of the drugs between the melted lipid and the aqueous phase [5]. This process minimizes the melting of the lipid phase and hence, the loss of hydrophilic drugs to the aqueous phases. The melted mixture of drug dissolved in a lipid is normally being solidified in a cold homogenization process. The solidified mixture is milled in liquid nitrogen or dry ice with the aid of a mortar mill. The grinded particles are then dispersed into an aqueous surfactant solution and disrupted by putting them once or several times through the homogenizer [6].

Solid Lipid Micro/Nano particles are also prepared by two major techniques namely: the ultrasonication or high speed homogenization. The ultrasonication and high speed homogenization is required for small particle sizes. Some of the disadvantages of this technique include potential contamination of the metal and physical instability [7]. The oral bioavailability of drug molecules could be improved by using some mechanisms. The phospholipids, bile salt and cholesterol are secreted from the gall bladder in response to the solid lipid micro/ nano particles entering the gastrointestinal tract [8]. A crude emulsion is formed by this product which improves the solubilization of lipophilic drugs. Lipids could generally cause a delay in the gastric emptying time, enabling the drugs to have better dissolution at the absorption site [9] Lipids are generally known to affect intestinal permeability by changing the gut wall permeability and its barrier function [10]. Also, first pass effect can be prevented, when the solid lipid micro/ nano particles through the lymphatic route, have access to the systemic circulation. Variable bioavailability and prolonged plasma levels could be achieved via the incorporation of drugs into lipid nanoparticles. The greatest flexibility in the modulation of the drug release profile within the gastrointestinal tract could be provided by this system and also protection against chemical degradation for thermolabile drug molecules [11].

The advantages of solid lipid micro/nano particles include:

i Controlled release of the drug.
ii Protection of the drug against chemical degradation
iii Physical and chemical storage stability
iv High tendency to use biodegradable lipids

Nevertheless, the disadvantages associated with solid micro/nanoparticles include: Particle growth, unexpected gelation tendency, drug loading limitation [12]. Futhermore, solid lipid micro/ nano particles have several clinical and pharmaceutical applications. SLMs have been used as a carrier of curcumin in the treatment of inflammatory bowel diseases [13]. Theophylline loaded solid lipid nanoparticles have been demonstrated to be of benefit in the pulmonary drug delivery. Solid lipid microparticles have also been employed in imaging example, perflaxane lipid microparticles is used in clinics or hospitals to determine gastrointestinal problem through the magnetic resonance imaging (MRI), to differentiate diseased structure from normal structures [14].

Self-emulsifying oil formulations (SEOFs)

Self-emulsifying oil formulation (SEOF) can also be described as self-emulsifying drug delivery system (SEDDS), self nano emulsifying drug delivery system (SNEDDS) and self micro emulsifying drug delivery system (SMEDDS). SMEDDS and SNEDDS form micro-emulsions and nano emulsions respectively in aqueous phase with droplet sizes of less than or equal to 100 nm while SEDDS are emulsions with droplet sizes of above 100 nm [15].

SEOFs consists of oils, surfactant and co-solvent that emulsifies spontaneously to produce fine oil in water emulsion when introduced into aqueous phase under gentle agitation (Patel et al., 2013). According to Jing- Ling et al (2007), SEOFs are defined as isotropic mixtures of natural or synthetic oils, surfactant and co-surfactant [16].

Another definition of SEOFs says that they are isotropic mixtures of drug, oil/lipid, surfactant and/or co-surfactant that normally form fine emulsion/ lipid droplets ranging in size from less or more than 100 nm on dilution with physiological fluid [17].

Medium chain triglyceride oils and non-ionic surfactants which are less toxic have also been formulated using SEOFs. On per oral administration, they form fine emulsion in the gastrointestinal tract provided by gastric motility [18]. Upon mild agitation, followed by dilution in aqueous media, such as gastrointestinal fluids, they form oil in water emulsion. Fine oil droplet would pass rapidly from the stomach and promote wide distribution of the drug throughout the gastrointestinal tract, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substance and the gut wall [19].

Upon spontaneous emulsification, SEOFs produce fine oil in water emulsion when introduced into an aqueous phase under gentle agitation. In the gastrointestinal tract and the gastrointestinal motility of the stomach, SEOFs spread readily and the intestine provide the necessary agitation for self emulsification. The advantage of this system is that the drug is in dissolved form and a large interfacial area for the drug absorption is provided by the small droplet size [20].

SEOFs are formulations that are highly stable. Lipophilic drug compounds are known to exhibit dissolution rate limited absorption which may offer an improvement in the rate and extent of absorption and result in more reproducible blood time profiles. Self-emulsification process proceeds through formation of liquid crystals and gel phases. The release of drug from SEOFs is dependent on liquid crystal formed at the interface, since it is likely to affect the angle of curvature of the droplet formed and the resistance offered for partitioning of drug into aqueous media. The effect of liquid crystals will be more prominent for semisolid or solid SEOFs because liquid crystal phase are formed *in situ* and the drug diffuses through liquid crystal phase into aqueous media.

Excipient selection

SEOFs consist of oil, surfactant and co-solvent or co-surfactants.

OIL: The oily component is a fatty acid ester or a medium /long chain saturated, partially unsaturated or unsaturated in liquid, semisolid or solid form at room temperature. They are the most important excipient because oil can solubilize the lipophilic drug in a specific amount and it can facilitate self-emulsification. The fraction of lipophilic drugs could be increased and transported via the intestinal lymphatic system. This could lead to increased absorption from the gastrointestinal tract [21].

In the formulation of SEOFs, long and medium chain triglycerides are used. Novel semisynthetic medium chain triglyceride oil has surfactant properties and is widely replacing the regular medium chain triglyceride [22]. These novel semisynthetic oils have amphiphilic properties and they include polyglycolized glycerides with varying fatty acids and polyethylene glycol chain length. Studies have shown that Labrasol® a member of the polyglycolized glycerides with HLB of 14 displayed the most satisfactory self-emulsification properties.

SURFACTANT: In the formulation of SEOFs, non-ionic surfactants with high hydrophilic-lipophilic balance (HLB) values are used. Examples include Labrafac CM-10, Tween, Labrasol, and Cremophore. Natural source emulsifiers are expected to be safer than synthetic ones. Surfactant strength ranges between 30-60 % w/w of the formulation in order to form stable SEOFs. Surfactant exhibit amphiphilic properties and they dissolve or solubilize relatively high amount of hydrophobic drug compounds. Surfactants that have high HLB and hydrophilicity assist the immediate formation of o/w droplet and rapid spreading of the formulation in the aqueous medium. The GIT could be irritated by large quantity of surfactant, and non-ionic surfactants have less toxicity as compared to ionic surfactants [23].

CO-SOLVENT: They are known to increase the solvent capacity of the formulation especially in those that contain a large amount of hydrophilic surfactant [24]. Co-solvents are also used to increase the solubility of active pharmaceutical ingredient above its normal limit within the formulation. When in contact with the gastrointestinal fluid and with subsequent self- emulsification of the formulation, the co-solvent diffuses into the aqueous phase. Use of high concentration of the co-solvent could lead to drug precipitation by dissociation. Examples of co-solvent include ethanol, Propylene Glycol, polyoxyethylene, propylene carbonate, Propylene Glycol Ether. However, alcohols and other volatile substance may not be suitable because they could migrate into the shell of soft and hard gelatin capsules resulting in precipitation of lipophilic drug.

Palm kernel oil

The four tropical regions that are known to plant oil palm nuts include; Africa, South East Asia, Latin

America and South Pacific [25]. The generation of oil is the main objective of the palm industries. Two major oils are extracted from the fruit. They include the palm oil and kernel oil. They both exhibit differences in applications, composition, properties. This oil could be extracted from the kernel of the fruit of the palm tree *Elaeis guineensis*, by mechanical pressing, without the use of solvents or other chemical substances. Palm kernel oil (PKO) is obtained from the kernel of the palm fruit and it is located inside the hard shell while the outer fleshy mesocarp gives palm oil [26]. PKO is similar to coconut oil in composition and both are the only source of lauric oil available in the world market. The fatty acid profile of palm kernel oil presented in percentages is as follows:

Table 1: Percentage Constituents of Palm kernel Oil

Fatty acids	Percentages (%)
Lauric acids (C 12:0)	48.2
Myristic acid (C14:0)	16.2
Palmitic acid (C16:0)	8.4
Capric acid (C10:0)	3.4
Caprylic acid (C8:0)	3.3
Stearic acid (C18:0)	2.5
Oleic acid (C18:1)	15.3
Linoleic acid (C18:2)	2.3
Others (Unknown)	0.4

Palm kernel oil (PKO) is more unsaturated and a wider range of products can be hydrogenated from it which could be used either alone or in blends with other oil for biscuit dough, filling creams, imitation whipping cream, cake icing, ice cream substitute chocolate and other coatings, sharp melting and melting margarines. Lauric acid, present in abundance in coconut oil is very important in the making of soap and a quality soap must contain at least 15 % lauric acids for quick lathering, while soap made from sea water is based on virtually 100 % lauric oils. Mostly, palm kernel oil are now used for the manufacture of short chain fatty acids, fatty amines, fatty alcohols, methyl esters, for use in detergents, cosmetics and many other cosmetic products but less consideration is given it for other purpose [27]. Palm kernel oil is a medium chain fatty acid. However, though this oil is locally available it has also found many applications in the formulation and development of stable lipid-based formulations.

Oleic acid

Oleic acid is a known fatty acid that is found naturally in various animal and vegetable fats and oils. It has peculiar lard like odor, colourless oil, although yellowish colour is associated with commercial samples. In chemical terms, oleic acid is classified as a monounsaturated omega-9 fatty acid, abbreviated with a lipid number of 18:1 cis-9. It has the formula $CH_3(CH_2)_7CH=CH(CH_2)_7COOH$. Oleic acid (18:1 0-9) is the mostly found in plants and animals. Its presence in microorganisms has also been recorded [28]. Oleic acid has a molecular weight of 282.47g/mole, specific gravity of 0.895, boiling point of 286.11°C and melting point of 16.3 °C. Oleic acid is soluble in methanol, diethyl ether, acetone, chloroform, most organic solvents, benzene, alcohol, carbon tetrachloride, and fixed and volatile oils. It is insoluble in cold water (MSDS of Oleic acid, 2012). They are used as an excipient in pharmaceuticals, in aerosol products, oleic acid is used as an emulsifying or solubilizing agent [29].

Solutol HS 15

The generic name of Solutol HS 15 is macrogol 15 hydroxystearate, polyoxyl 15 hydroxystearate. Solutol HS 15 is a non ionic solubilizer and emulsifying agent obtained by reacting 15 moles of ethylene oxide with 1 mole of 12 – hydroxyl stearic acid. It is a yellowish white paste at room temperature and becomes liquid at about 30 °C. The critical micelle concentration (CMC) lies between

0.005 and 0.02 %. Its HLB lies between 14 to 16. Solutol HS 15 consist of polygylcol mono and diesters of 12 – hydroxystearic acid (lipophilic part) and about 30 % of free polyethylene glycol (hydrophilic part). Solutol HS 15 is soluble in water, ethanol and 2- propranol to form a clear solution, but it is insoluble in liquid paraffin. This product nevertheless has wide use in pharmacy as non – ionic solubilizer for manufacture of aqueous parenteral preparation with vitamins and lipophilic actives [30].

Tween 80

Tween 80 also known as polyoxyethylenesorbitan mono-oleate Polysorbate 80, Sorbitan monoleate, is a polyethylene sorbitol ester, with a calculated molecular weight of 1,310 Daltons, assuming 20 ethylene oxide units, 1 sorbitol, and 1 oleic acid as the primary fatty acid. Fatty acid constituents of this product are determined by trans-esterification to yield fatty acid methyl esters, which are identified by gas chromatography. Typically, the fatty acid composition is approximately 70% oleic acid with several other fatty acids such as palmitic acid indicated. Tween 80 has specific gravity of 1.07, HLB (Hydrophile – lipophile balance) values of 15.0, critical micellar concentration (CMC) of 13 – 15 mg/liter, and has good solubility in water. Tween 80 is used both as a dispersing and emulsifying agent in medicinal and food product. However, Tween 80 (or polysorbate 80 is a nonionic surfactant that is hydrophilic in nature. It is the most commonly used surfactant and it has been shown to enhance solubility of compounds leading to increased absorption of drug candidates [31]. It is a common excipient in various human dosage forms. However, recent reports suggested that it is capable of enhancing the permeability of numerous drugs in vitro in Caco-2 cell [32]. It has little or no activity as an antibacterial agent and emulsifying and dispersing substances in medicinal and food products. It has little or no activity as an anti-bacterial agent. Polysorbates have been reported to be incompatible with alkalis, heavy metal salts, phenols, and tannic acid. They may reduce the activity of a lot of many preservatives.

Capryol PGMC

Capryol PGMC, a water insoluble surfactant with HLB of 5, is also a product of Gattefossé. Historically, a water insoluble surfactant is described as co-surfactant in gattefossé documents [33]. The chemical name of Capryol PGMC is Propylene Glycol monocaprylate. Gattefossé excipients are obtained by the esterification of fatty acids with alcohol glycerol, polyethylene glycol, polyglycerol, propylene glycol. Low HLB excipients have a higher proportion of glycerides, a lower concentration of free PEG, exhibit lower water solubility. Capryol pgmc like other gattefossé excipients are amphiphilic in nature due to the lipophilic fatty acid portion and the hydrophilic alcohol portion. The amphiphilicity of lipid excipient is expressed as the hydrophilic – lipophilic balance value. According to the gattefossé handbook 2010, Capryol PGMC can be used in the formulation of LFCS type II emulsion which is a mixture of oils and water insoluble surfactants.

Biopharmaceutical issues

The oral bioavailability of drugs could be affected by lipids. This is achieved by changing biopharmaceutical properties such as increasing dissolution rate and solubility in the intestinal fluid, protecting the drug from chemical as well as enzymatic degradation in the oil droplet and the formation of lipoproteins promoting lymphatic transport of highly lipophilic drug [34]. The chain length of the triglyceride, is dependent on the absorption profile and the blood/lymph distribution of drug depend on saturation degree and the volume of lipid administration.

The various methods used by lipids in increasing the bioavailability of drugs include [35]:

1. Reduction in gastric transit time, thereby slowing delivery to the absorption site and increasing the time available for dissolution.

2. Effective luminal drug solubility increase: Lipids in the GI tract are known to stimulate an increase in the secretion of bile salts (BS) and endogenous biliary lipids including phospholipids (PL) and cholesterol leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilisation capacity of the GI tract.

3. Stimulation of the intestinal lymphatic transport: lipids may enhance the extent of lymphatic transport and increase the bioavailability directly or indirectly via a reduction in first pass metabolism especially for lipophilic drugs. Drugs are transported to the systemic circulation in association with the lipid core of lipoproteins especially for those processed by the intestinal lymph [36].

4. A Change in the biochemical barrier function of the GI tract: Certain lipids and surfactants are known to attenuate the activity of the intestinal efflux transporters as indicated by the P-glycoprotein efflux pump and may also reduce the extent of enterocyte-based metabolism.

5. Changes in the physical barrier of the GI tract: Various combinations of surfactants lipids, lipid digestion products have been shown to have permeability enhancing properties.

Mechanisms of self-emulsification

Emulsification occurs when the entropy changes that favours dispersion is greater than the free energy required to increase the surface area between the oil and aqueous phase of the dispersion. Self-emulsifying process is related to free energy, ignoring the free energy of mixing can be expressed as below

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

Where ΔG – free energy associated with the process, N_i- Number of droplets of radius r, σ - interfacial energy [42].

According to Shehata (2008), the free energy of an emulsion is a direct function of the energy essential to create a new surface between oil and water phase [37].

Self-emulsification occurs rapidly usually at low interfacial tension. However emulsion is usually thermodynamically unstable as the oil phase and the aqueous phase will tend to separate with time to reduce the interfacial area and also free energy of the system. The emulsifier is known to reduce interfacial tension by forming a barrier around the oil droplets and hence the free energy of the systems [38]. A monolayer of emulsion droplets is usually formed by the emulsifying agents and hence reduce the interfacial energy thereby preventing coalescence.

For self-emulsification, introduction of the oil phase into the aqueous phase with gentle agitation, will cause the aqueous phase to penetrate through the interface into the oil phase until the interface of the two phases is disrupted. This will cause oil droplets to form, which then results in emulsification. The ease of emulsification is governed by the ease of water penetration into the various liquid crystals or gel phases formed on the surface of the droplets. The free energy required to form emulsion in self-emulsifying systems is very low and positive or negative. Emulsification requires a little energy input and also involves the destabilization through contraction of local interfacial region.

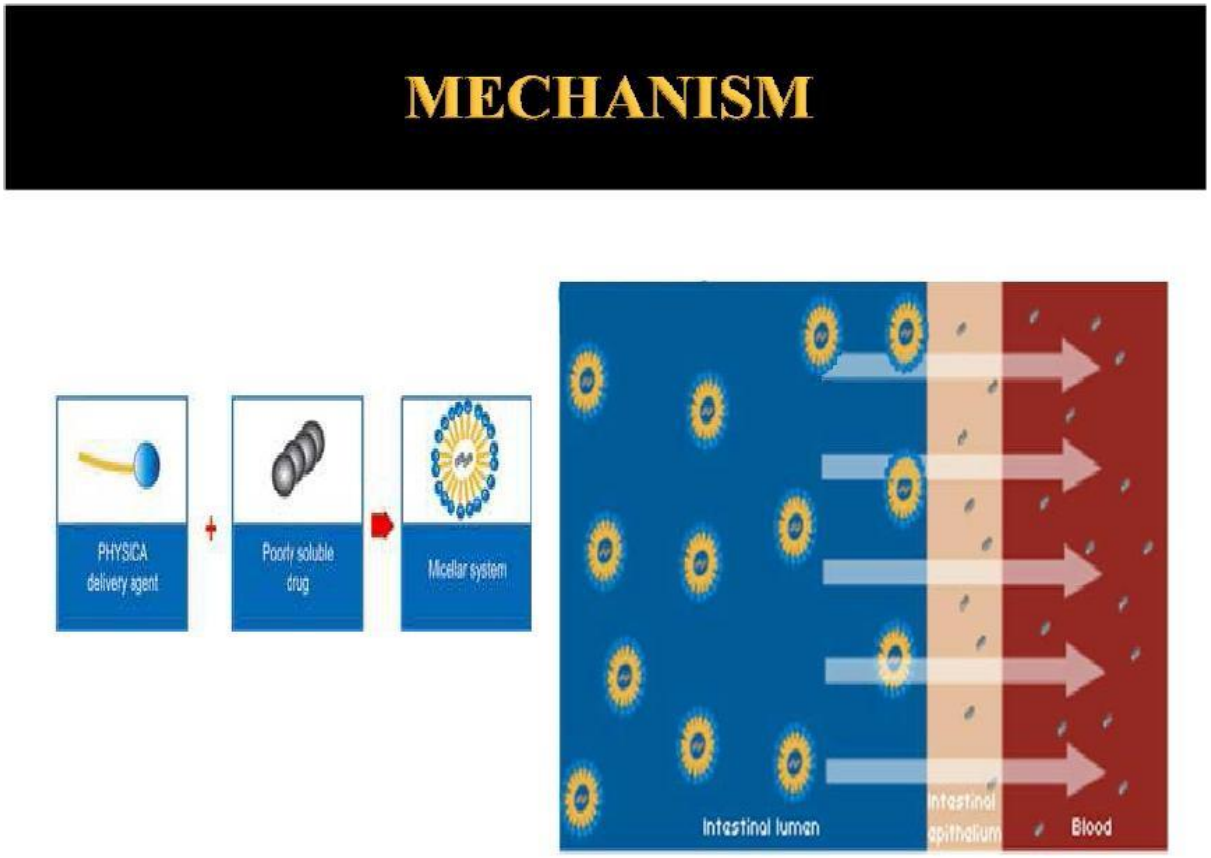

Fig. 2: Mechanism of self-emulsification [39].

Factors that affect SEDDs

1 Polarity of the lipophilic phase: The release of drug from microemulsion, is affected by the polarity of the lipid phase. The concentration of the emulsifier governs the polarity of the droplets. Therefore the affinity of the drug for oil, is affected by the polarity and also the type of forces involved. High polarity will lead to the rapid release of drug into the aqueous phase [40].

2. Nature and Dose of the drug: Good solubility is very essential for high dose drugs to be used in the formulation of SEDDs. The solubility of the drug in the oily phase, is affected by The ability of SEDDs to maintain the drug in solubilized form.

Evaluation and characterization of SEDDs

Self-emulsification is the very essence of SEEDs and can be assessed visually. Determining the rate of emulsification, droplet size distribution and turbidity measurement can be attributed to the efficiency of self-emulsification [41].

Thermodynamic studies

The precipitation of the drug in the excipient matrix, can affect the physical stability of a lipid –based formulation. Poor formulation leads to phase separation of the excipient, affecting both the formulation performance and visual appearance as well. Incompatibilities between the formulation and the gelatin capsules shell can lead to incomplete drug release, brittleness or deformation, delayed disintegration.

Thermodynamic studies can be carried out in three ways:

1. Heating cooling cycle method: This involves the six cycles between refrigerator temperature (4 °C) and 45 °C with storage at each temperature of not less than 48 h is studied. Formulations that are stable at this temperature, are subjected to centrifugation test.

2. Centrifugation Test method: formulations that passed the heating cooling cycle method are centrifuged thaw cycles between 21 °C and +25 °C with storage at each temperature for not less than 48 h is done at 3500 rpm for 30 min. If phase separation is absent in these formulations, then they are taken for the freeze thaw stress test.

3. Freeze thaw cycle method: The absence of phase separation, creaming or cracking shows that the formulation passed the test with good stability [42].

Dispersibility test

USP XXII dissolution apparatus 2 can be used to study the efficiency of self-emulsification of oral nano or micro emulsion. One milliliter of each formulation was added to 500 mL of water at 37 ± 0.5 ^{0}C. Gentle agitation is been provided by a standard stainless steel dissolution paddle rotating at 50 rpm. The following grading system is used to access the in vitro performance of the formulations.

Grade A: nanoemulsion that forms rapidly, having a clear or bluish appearance.

Grade B: Nanoemulsions that form rapidly, slightly less clear emulsion, having a bluish white appearance.

Grade C: emulsions that form fine milky appearance, which 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, that exhibit poor or minimal emulsification with large oil globules present on the surface. Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT.SEDDS fall within Grade C category [43].

Turbidimetric evaluation

The growth of emulsion can be monitored using the nephelo-turbidimetric evaluation. 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 plate at ambient temperature, a turbidimeter is used to measure the increase in turbidimetry. It is not possible to monitor the rate of change of turbidity (rate of emulsification) because the time required for complete emulsification is too short [44].

Viscosity determination

A soft gelatin or hard gelatin capsule is used in the administration of SEEDS. It should exhibit easy pourability into capsules and such system should not be too thick to create a problem. Brookfield viscometer is used to determine the rheological properties of the micro emulsion. The essence of the viscosities determination is to confirm whether the system is w/o or o/w. If a system has a high viscosity, then it is w/o type. If the system has low viscosity, then it is o/w type of the system [45].

Droplet size analysis/ particle size measurements

Photon correlation spectroscopy is used to determine the droplet size of the emulsions (which analyses the fluctuations in light scattering due to Brownian motion of the particles) using a Zeta sizer which is used to measure sizes between 10 and 5000 nm. At 25 °C at a 90° angle, light scattering is monitored after external standardization with spherical polystyrene beads. Even after 100 times dilution with water, the nanometric size range of the particle is

retained which proves the system's compatibility with excess water.

Refractive index and percent transmittance

The transparency of formulation could be proved using the refractive index and percent transmittance. The refractive index of the system is measured by refractometer by placing drop of solution on slide and it compare with water (1.333). UV-spectrophotometer is used to measure the percent transmittance of the system at a particular wavelength using distilled water as blank. The transparent nature is determined when the refractive index of system is similar to the refractive index of water (1.333) and formulation have percent transmittance > 99 percent.

Electro conductivity study

Ionic or non-ionic surfactant, oil, and water constitute the SEED system. This test is used to determine the electro conductive nature of system. The electro conductivity of resultant system is measured by electro conductometer. In conventional SEDDSs, presence of free fatty acids causes the charge on an oil droplet to be negative.

***In vitro* diffusion studies**

This test is usually carried out to study the drug release behaviour of formulation from liquid crystalline phase around the droplet using dialysis technique.

Drug content

Suitable solvent could be used for dissolving drug from pre-weighed SEDDS. Drug content in the solvent extract was analyzed by suitable analytical method against the standard solvent solution of drug.

Advantages of SEDDs

Oral delivery of poorly water-soluble compound involves the dissolution of the compound in a suitable solvent and fill the formulation into capsules. The benefit is to overcome the initial rate limiting step of particulate dissolution in the aqueous environment within the GIT. 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. Less potential for precipitation is achieved when you dissolve the dug in a lipid vehicle. On dilution within the GI tract, partitioning kinetics will favor the drug remaining in the lipid droplets [46].

Major advantages of SEEDS include:

1. Enhanced oral bioavailability, subsequently leading to dose reduction.
2. Sensitive drugs are protected.
3. Increased drug absorption
4. Drug targeting specificity towards specific absorption window in GIT
5. Protection of drugs from the gut environment
6. Control of drug delivery profile
7. Reduction in variability including food effects
8. High drug loading efficiency.

Application of SEDDs

Improvement in Solubility and Bioavailability: Drugs incorporated in SEDDS leads to increase in solubility due to the fact that it circumvents the dissolution step in case of class II drugs. A typical example is ketoprofen moderately hydrophobic NSAIDs, which is formulated as sustained release. With its formulation as sustained release, there was a reported case of incomplete release from the formulation. Attempts to put the drug into other advanced formulation still had the challenges of instability, processing and economic problems.

This problem can be successfully overcome when ketoprofen is presented in SEDDS formulation. This formulation enhances bioavailability due to increase in drug solubility and decrease in gastric irritation. In SEDDS, the lipid matrix interacts readily in water forming fine particulate oil in water o/w emulsion. These emulsion droplets will deliver the drug to GIT mucosa in dissolved state readily accessible for absorption [47].

Protection against Biodegradation: self-emulsifying drug delivery system are known to reduce degradation as well as improve absorption. This may be especially useful for drugs for which low solubility and degradation in the GIT contribute to a low oral bioavailability. The acidic pH in the stomach is responsible for the degradation of drugs in physiological system due to enzymatic or hydrolytic degradation. Presentation of drugs in the form of SEDDS, increases the protection of these drugs against these degradation processes as liquid crystalline phase in SEDDS might be an act of barrier between the degrading environment and the drug. For instance aspirin shows high degradation in the GI tract, because it is readily hydrolyzed to salicylic acid in an acid environment. When formulated in galacticles oral lipid matrix system, it showed the good plasma profile when compared to reference standard formulation. The oral bioavailability of undegraded acetylsalicylic acid was improved by 73 % by the galacticles oral lipid matrix system formulation compared to the reference formulation. This suggests that the SEDDS formulation has a capacity to protect the drug from degradation in the GIT [48].

Solid SEDDs (S-SEDDs)
One of the limitations of SEDDS is that many excipients used in SEDDs are not solid at room temperature. The existence of SEDDS in solid state has also been reported. Given the advantage of solid dosage forms, S-SEDDs have been extensively exploited in recent years as they frequently represent more effective alternatives to conventional liquid SEDDs.

S-SEDDs are solid dosage forms that have self – emulsification properties. S-SEDDs involves the incorporation of liquid or semi solid SE ingredient into powders or nanoparticles by different solidification techniques. To a large extent S-SEDDs are combination of SEDDs and solid dosage form, so many properties of S-SEDDs are the sum of the corresponding properties of both SEDDs and solid dosage forms. For instance the characterization of SE pellets contains not only the assessment of self emulsification but also friability, surface roughness and so on.

SEDDs are usually in form of SE capsules, SE solid dispersion and dry emulsion, but other solid SEDDS also exists such as SE pellets/tablet, SE microspheres/nanoparticles and SE suppositories/implants [49].

Solidification techniques
Techniques are chosen on the basis of the properties of lipid excipients**.** The transformation of liquid or semisolid formulation into solid particles is common with some of the techniques. (Powder, granules, or pellets) which could subsequently be filled into capsules, sachet or compressed into tablets. These solidification techniques include:
-Capsule filling
-Spray drying
- Solid surfaces Adsorption
-Melt granulation
-Melt extrusion/extrusion spheronization

Capsule filling Technique
This technique is used for the encapsulation of liquid/semisolid SE formulation via oral route. Four step processes are involved for semi-solid formulations. They include the : semisolid excipient is heated to at least 20 ^{o}C above its melting point, Incorporation of the active substance while stirring, Capsule filling with molten mixture, cooling of the formulation to room temperature . For the liquid formulation it involves a two step process: 1) capsule filling with the formulation 2) Sealing the body and the cap of the capsule either by bending or by microspray sealing. The main consideration in capsule filling is the issue of compatibility of the excipient with the capsule shell. The advantages of capsule filling are simplicity of manufacturing, suitability for low dose highly potent drugs and high drug loading potential.

Spray drying
In this method, the formulation is being prepared by mixing lipids, surfactants, drugs, solid carrier and solubilisation of the mixture before spray drying [50]. Spray drying is defined as a process by which a liquid solution is sprayed into hot air chamber to evaporate the volatile fraction [51].The liquid formulation that is solubilized, is then atomized into a spray of droplets. The droplets that are formed are introduced into a drying chamber, where the volatile phase evaporates forming dry particles under controlled temperature and airflow condition. Such particles can be further prepared into tablet/ capsule. The atomizer, the temperature, the most suitable airflow pattern, and the drying chamber design are selected according to the drying characteristics of the product and powder specification.

Adsorption to solid surface
The adsorption process is used to obtain free flowing powders from liquid SE formulation by adsorption to solid carriers. The adsorption process is a simple step method and just involves addition of the liquid formulation onto carriers by mixing in a blender. The resulting powder may then be filled directly into capsules or alternatively, mixed with suitable excipients before compressing into tablets. A significant benefit of the adsorption technique is Good content uniformity. SEDDs can be adsorbed at high levels (up to 70 % (w/w) onto suitable carriers [52]. Solid carriers can be microporous inorganic substances, high surface-area colloidal inorganic adsorbent substances, cross-linked polymers or nanoparticle adsorbents, for example, silica, silicates, magnesium trisilicate, magnesium hydroxide, talcum, crosspovidone, cross-linked sodium carboxymethyl cellulose and crosslinked polymethyl methacrylate. Cross-linked polymers create a favourable environment to sustain drug dissolution and also assist in slowing down drug re-precipitation. This adsorption has been successfully applied to gentamicin and erythropoietin with caprylocaproyl polyoxyl glycerides (Labrasol®) formulation [53].

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. As 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. Moreover, it is also a good alternative to the use of solvent. Melt granulation or palletization is a process that allows the transformation of a powder mix containing the drug into granules or spheronized pellets [54].The main parameters that control the granulation process are impeller speed, mixing time, binder particle size, and the viscosity of the binder. A wide range of solid and semisolid lipids can be applied as meltable binders. Gelucire1, a family of vehicles derived from the mixtures of mono-/di-/tri-glycerides and polyethylene glycols (PEG) esters of fatty acids, is able to further increase the dissolution rate compared with PEG usually used before, probably owing to its SE property [55]. Other lipid-based excipients evaluated for melt granulation to create solid SEDDs include lecithin, partial glycerides, or polysorbates. The melt granulation process was usually used for adsorbing SES (lipids, surfactants, and drugs) onto solid neutral carriers (mainly silica and magnesium aluminometa silicate) [56].

Melt extrusion/extrusion spheronization

Melt extrusion is defined as a solvent-free process that allows high drug loading (60 %), as well as content uniformity. Extrusion is a procedure 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 extruder aperture will determine the approximate size of the resulting spheroids. The extrusion–spheronization process is commonly used in the pharmaceutical industry to make uniformly sized spheroids (pellets).The extrusion–spheronization process requires the following steps: dry mixing of the active ingredients and excipients to achieve a homogenous powder; wet massing with binder; extrusion into a spaghetti-like extrudate; spheronization from the extrudate to spheroids of uniform size; drying; sifting to achieve the desired size distribution and coating (optional). In the wet masses comprising SES (polylobate 80 and mono-/di-glycerides), lactose, water and MCC, the relative quantities of SES and water had a significant effect on the extrusion force, size spread, disintegration time, and surface roughness of pellets. Studies suggested that the maximum quantity of this SES that can be solidified by extrusion spheronization occupies 42% of the dry pellet weight [57]. Generally, the higher the water level, the longer the disintegration time. The rheological properties of wet masses may be measured by an extrusion capillary. It has been shown that SES containing wet mass with a wide range of rheological characteristics can be processed, but a single rheological parameter cannot be used to provide complete characterization of how well it can be processed by extrusion–spheronization. This approach has been successfully tried for 17 β-estradiol and two model drugs with surfactants such as sucrose monopalmitate, lauroylpolyoxylglycerides and Polysorbate 80 (Tween® 80).Gelucire® 44/14 to be used directly in the core of the formulation matrix. An innovative "system-incylinder" molding technique was recently employed to develop a dual purpose (enhanced bioavailability and controlled release) formulation with propranolol hydrochloride. Melt extrusion is a solvent free process that allows high drug loading as well as content uniformity for low dose high potency active [58].

Dosage form development from SEOFs

The liquid SEOFs can be transformed into various solid dosage forms. These include:

- Self emulsifying capsules
- Self emulsifying sustained / controlled release tablets
- Self emulsifying solid dispersion
- Self emulsifying beads
- Self emulsifying sustained release microspheres
- Self emulsifying nanoparticles
- Self emulsifying suppositories
- Self emulsifying implants

Self emulsifying capsules.

The simplest and the most common technology used for the encapsulation of liquid, semisolid or solid SE formulations for oral route is capsule filling. When liquid formulations are to be encapsulated, two step processes are usually involved:

Filling of the capsules with the liquid formulation

Sealing of the body and cap of the capsule by banding or microspray sealing [59].

An alternative method is the incorporation of liquid self emulsifying ingredients into powder, such that it is incorporated into capsules. Shikha et al (2009) reports that the self emulsifying pellet formulation of progesterone, prepared by the process of extrusion / spheronization showed good *in vitro* drug release of 100 % within 30 min and T 50 % at 13 min [60]. After administration of capsules containing conventional liquid SE formulations or the solid self emulsifying formulations, emulsion /nanoemulsion /microemulsion droplets form and subsequently disperse in the GI tract to reach sites of absorption.

The advantages of capsule filling include simplicity of manufacturing, suitability for highly potent low-dose drugs, and high drug loading (up to 50 % w/w) potential.

Self-emulsifying sustained / controlled release pellets

Pellets are multiple unit dosage form which possess many advantages over conventional solid dosage forms, such as flexibility in manufacturing, reduction of intrasubject and intersubject variability of plasma profiles, and minimizing GI irritation without lowering drug bioavailability. Thus, combining the advantages of pellets with those of the self emulsifying oil formulation by Self Emulsifying pellets is very interesting. Self emulsifying controlled-release pellets were prepared by incorporating drugs into self emulsifying system that enhanced their rate of release and then by coating the pellets with a water-insoluble polymer which reduced the rate of drug release. Pellets can be prepared by extrusion/spheronization. The combinations of coating and self emulsifying system could control *in vitro* drug release and provide a range of release rates. Franceschinis, (2005) reported the preparation of self-emulsifying pellets by wet granulation of powder mixture composed of microcrystalline cellulose, lactose and nimesulide as model drug with a mixture containing mono- and di-glycerides, Polysorbate 80 and water, in a high shear mixer [61]. Improvement in the permeation performance of the pellets composed of oil: surfactant in the ratio 1: 4 was also reported. Nitrendipine self emulsifying pellets were prepared via extrusion/spheronization technique, using the liquid SEOFs (comprising Miglyol 812, Cremophor RH 40, Tween 80 and Transcutol P) and adsorbents (silicon dioxide and crospovidone), microcrystalline cellulose and lactose. It was discovered that the area under the curve (AUC) of nitrendipine from the SE pellets was 1.6-fold greater than the conventional tablets and no significant difference compared with the liquid SEOFs [62].

Self-emulsifying solid dispersion

These involve the dispersion of drug in self-emulsifying solid excipients. The dosage form preparation involves, dissolving of drugs in melted carriers and the filling of the molten solutions into gelatin capsules. Because of the simplicity of manufacturing and scale up processes, the physicochemical properties are expected to change significantly during the scale up [63]. Solid dispersions is one of the formulation strategy that could increase the dissolution rate and bioavailability of poorly water-soluble drugs, however some manufacturing difficulties and stability problems still exist. Serajuddin pointed out that these difficulties could be surmounted by the use of SE excipients. These excipients have the capacity to further increase the absorption of poorly water-soluble drugs compared to previously used PEG solid dispersions. It could be filled directly into hard gelatin capsules in the molten state, thus avoiding the former requirement for milling and blending before filling [61]. SE excipients like Gelucire 44/14, Gelucire 50/02, Labrasol, Transcutol and TPGS (tocopheryl polyethylene glycol 1000 succinate) have been widely used in the preparation of self emulsifying solid dispersions [64]. Gupta et al (2013) reports the preparation SE solid dispersion granules using the hot-melt granulation method, in which seven drugs were studied with gelucire 50/13 as the dispersion carrier and Neusilin® US2 as the surface adsorbent [59].

Self-emulsifying beads

Self-emulsifying system can be formulated as a solid dosage form by using minimum amounts of solidifying excipients. Patil and Paradkar formulated loratidine loaded self emulsifying system and explored the possible use of porous polystyrene beads as carriers through the solvent evaporation method [65]. The porous polystyrene beads were produced by copolymerizing styrene and divinylbenzene. Thus the porous polystyrene beads has a complex internal void structure, is inert and stable over a wide range of pH, temperature and humidity. Though the bead size and pore architecture of the porous polystyrene beads affected the loading efficiency of the drug and its *in vitro* release, it still offers great potential as a carrier for solidification of Self emulsifying systems.

Self-emulsifying sustained release microspheres

Solid Emulsifying sustained release microsphere is also another dosage form developed from the liquid self emulsifying systems. You et al (2006) prepared solid self-emulsifying sustained release microspheres of zedoary turmeric oil, a traditional Chinese medicine with tumor suppressive, antibacterial and antithrombotic effects [65]. The zedoary turmeric oil was used as the oil phase and the solid self emulsifying sustained release microspheres were prepared using the quasi-emulsion solvent diffusion method involving the spherical crystallization technique. It was also discovered that the release of the turmeric oil from the dosage form was dependent on the ratio of hydroxylpropyl methyl cellulose acetate succinate to aerosol 200 in the formulation. After oral administration in rabbits, the sustained release microspheres showed higher bioavailability

when compared to the conventional liquid self emulsifying system.

Self-emulsifying nanoparticles

Techniques used in the production of nanoparticles can be used in the preparation of self emulsifying nanoparticles. The solvent injection method is one of the most widely used techniques. In this method, the lipid, surfactant, and drugs are melted together and injected dropwise into a stirred nonsolvent. The resulting SE nanoparticles are filtered out and dried. This approach yielded nanoparticles (about 100 nm) with a high drug loading efficiency of 74 %. An alternative technique is the sonication emulsion-diffusion-evaporation. The mixture of polylactide-co-glycolide (PLGA) and O-carboxymethyl-chitosan (O-CMC) had a Self Emulsifying effect, with no need to add another surfactant stabilizer. Eventually the 5-FU and plasmid encapsulation efficiencies were found to have 94.5% and 95.7%, respectively, and the 5-FU release activity from the nanoparticles was found to have sustained for three weeks [64].

Self-emulsifying suppositories

Solid self emulsifying systems can also be used via the rectum or vagina. Glycyrrhizin which barely reaches therapeutic plasma concentration when administered orally can achieve satisfactory therapeutic levels for chronic hepatic diseases via either vaginal or rectal self emulsifying suppositories. Takada and Murakami were able to formulate glycyrrhizin self-emulsifying suppositories with the mixture of C6 – C18 fatty acid glycerol ester and a C6 – C 18 fatty acid macrogol ester. Gugulothu et al. (2008) also formulated self-microemulsifying suppositories of artemether with faster onset of action and prolonged effect to be administered by rectal route [50]. The developed self-microemulsifying suppositories could sustain the activity (94%) for 20 days post infection. The survival of animals was also better as compared to the conventional formulation.

Self-emulsifying implants

Research into self-emulsifying implants has greatly enhanced the use and application of solid self emulsifying system. For instance, 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. Gugulothu et al (2008) prepared 1, 3-bis (2-chloroethyl)-1- nitrosourea (BCNU) self emulsifying drug delivery system for the sake of improving stability. The self emulsifying system was formulated with tributyrin Cremophor RH 40 (polyoxyl 40 hydrogenated castor oil) and Labrafil 1944 (polyglycolyzed glyceride). Then the self-emulsified BCNU was fabricated into wafers with flat and smooth surface by compression molding. The self-emulsified (SE) BCNU was loaded into poly (d,l-lactide-co-glycolide (PLGA) wafer as a new polymeric implant. *In vitro* release of BCNU was prolonged for about 7 days from SE BCNU-loaded PLGA wafer and it followed first order release kinetics. The final result depicts SE BCNU degraded much more slowly than the intact BCNU in PLGA matrix at 25°C [51].

Conflict of interest

The authors declare no conflict of interest.

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