The Pharmaceutical and Chemical Journal, 2022, 9(2):77-89

Available online www.tpcj.org

Review Article

ISSN: 2349-7092
CODEN(USA): PCJHBA

Self-emulsifying Drug Delivery System: An Overview with Novel Perspective

Deepshikha Kukde[1*], Meenakshi Bharkatiya[2]

[1]Research Scholar, Bhupal Nobles' University; Udaipur (Raj.), India.
[2]Associate Prof., Department of Pharmacy, B. N. Institute of Pharmaceutical Sciences, B.N. University; Udaipur (Raj.), India.
*Corresponding Author E-mail: meenakshibharkatiya@rediffmail.com

Abstract Self-emulsifying drug delivery systems, which are isotropic mixtures of oils, surfactants, solvents, and co-solvents or surfactants, may be used to design formulations to boost oral absorption of highly lipophilic drug compounds. It may be orally administered in soft or hard gelatin capsules. These systems form fine emulsions or micro-emulsions in the gastro-intestinal tract with mild agitation provided by gastric mobility. These formulations were increased bioavailability due to increasing the solubility of the drug and minimize gastric irritation. The very fact is that almost 40% of the new drug compounds are hydrophobic implies that studies with a Self-emulsifying drug delivery system will continue, and a lot of drug compounds were developed as a Self-emulsifying drug delivery system can reach the pharmaceutical market in the upcoming future. This review stated the mechanism of self-emulsification, composition, formula approaches, completely special techniques, evaluation, and factors poignant Self-emulsifying drug delivery system, advantages, disadvantages, applications, and future traits in self-emulsifying drug delivery systems.

Keywords Self-emulsifying drug delivery systems, lipophilic drugs, isotropic, emulsions, surfactant concentration, and bioavailability

Introduction

In recent years, the formulation of poorly soluble compounds has presented fascinating challenges for formulation scientists in the pharmaceutical business. Up to the current chemical entities discovered by the pharmaceutical business square measure poorly soluble or lipophilic compounds that lead to poor oral bioavailability, high Intra and inter-subject variability, and lack of dose proportion.

To overcome these problems, varied formulation methods square measure exploited and the employment of wetter, macromolecule permeation enhancers, micronization, salt formation, cyclodextrins, nanoparticles, and solid dispersions. Recently, much interest has been paid to lipid-primarily based formulations totally, with unique pressure on self-emulsifying drug delivery system (SEDDSs), to reinforce the oral bioavailability of lipophilic drugs [1].

Self-emulsified drug delivery system formulations may be simple binary systems. Lipophilic phase and drug or lipophilic phase, surfactant, and drug or medicine [2]. The formation of self-emulsifying drug delivery systems requires the use of a co-surfactant to generate a microemulsion. Self-emulsifying drug delivery systems formulations are characterized by *in vitro* lipid drop sizes of 200 mm to 5 mm, and therefore the dispersion has a turbid appearance. Self-emulsifying formulations are combos of oils and surfactants, preferably isotropic, and on occasion

containing co solvents, which emulsify spontaneously to produce fine oil in water emulsions when introduced into the aqueous phase under gentle agitation [3, 4]. Recently, Self-emulsifying drug delivery systems have been developed using medium-chain tri-glyceride oils and non-ionic surfactants, the latter being less toxic [5, 6, 7].

Self-emulsifying drug delivery systems are used to solve low bioavailability problems of poorly soluble & highly permeable compounds. Hydrophobic tablets can be dissolved in those formulations, allowing them to be administered as a unit dosage configuration for per-oral management. When self-emulsifying drug delivery systems formulation is released in the lumen of the gastrointestinal tract, they come in contact with GI fluid and form a fine emulsion (micro or nano) so-called *in situ* emulsification or self-emulsification which further leads to solubilization of drug that may subsequently be absorbed by lymphatic pathways, bypassing the hepatic first-pass effect. This bioavailability enhancing property has been associated with several *in vivo* properties of the lipid formulations, including [8]:

- Formation of fine dispersions and micelles suspensions to prevent precipitation and recrystallization of the drug substance.
- The ability of certain lipid compounds and therefore their metabolites to initiate changes in the gastrointestinal fluid to favor improved drug absorption.

Some lipid carriers are associated with selective drug absorption in the lymphatic transport system, reducing the effectiveness of first-pass drug metabolism.

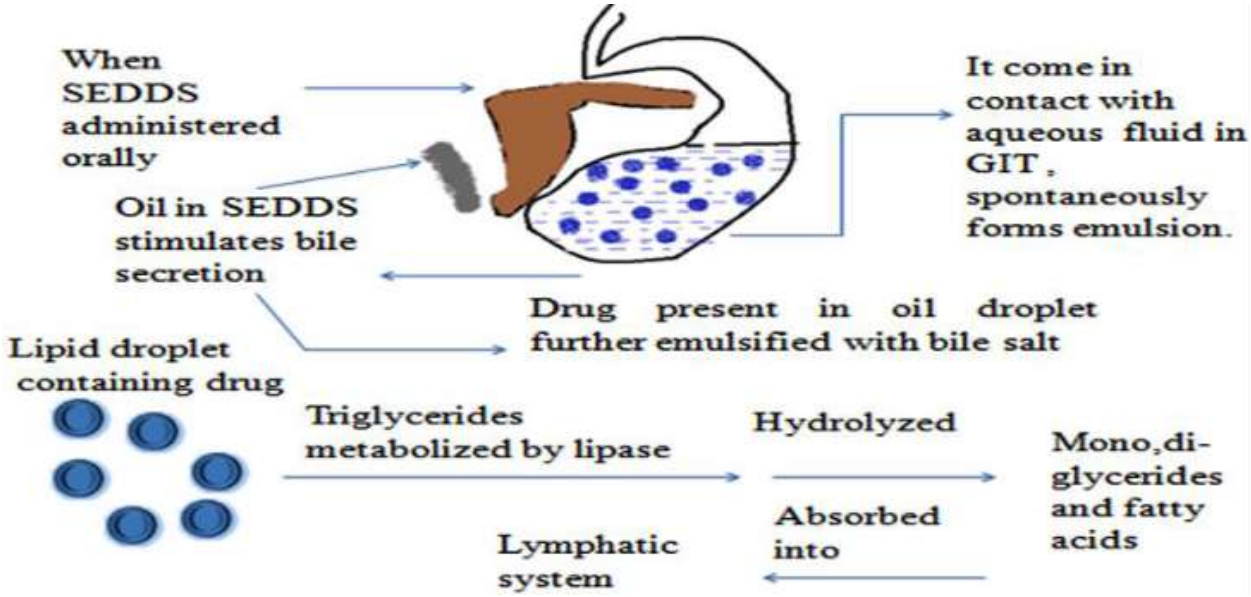


Figure 1: Self emulsification process

Self-Nano Emulsifying Drug Delivery System: Self-nano emulsifying drug delivery systems are nano-emulsions formed by self-emulsifying drug delivery systems. This is particularly necessary for drugs for increasing solubility such as simvastatin, atorvastatin [9].

Self-Micro Emulsifying Drug Delivery System: - Self-Micro Emulsifying Drug Delivery Systems are micro-emulsions formulated with the aid of using the self-emulsifying drug formulation. It is thermodynamically strong and paperwork optically apparent emulsion. The main distinction between micro-emulsions and not unusual place emulsions is precisely because of the particle size of depths. The length of the drops of not unique place emulsion degrees among 0.2 and 10 μm, and that of the depths of microemulsion shaped with the aid of using the self-micro emulsifying drug delivery typically degrees among two and a hundred nm. Since the particle length is small, the entire floor location for absorption and dispersion is notably prominent than that of stable dosage form, and it could effortlessly penetrate the gastro-intestinal tract and be absorbed. The bioavailability of medication is consequently progressed [10].

A schematic about 'self-micro emulsifying drug delivery systems is shown in Figure 2.

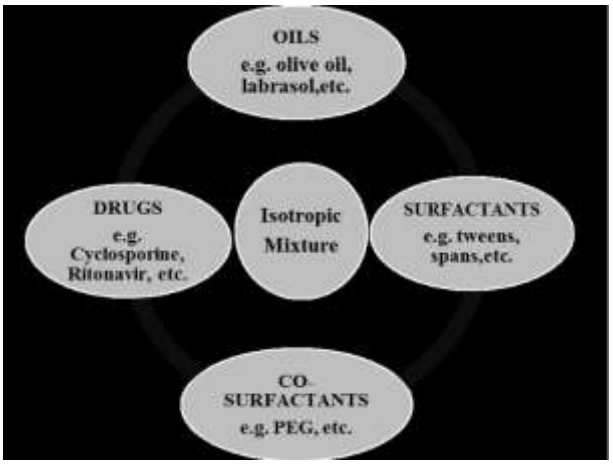


Figure 2: Illustration of what is self-emulsifying drug delivery system

It has been recommended that self-emulsifying drug delivery systems may be prepared, which after oral administration in gelatin capsules, will emulsify inside the gastric contents [11].

The advantage of self-emulsifying formulations over solid dosage formulations is that the dodging of slow drug dissolution. The distribution of the emulsion in the GIT helps to prevent irritancy.

Properties of SEDDS [12]:

1. They will self-emulsify quickly in gastro-intestinal fluids & under the influence of gentle agitation provided by peristaltic and different movements of the gastro-intestinal tract, they form a fine o/w emulsion.
2. They will effectively incorporate drugs (hydrophobic or hydrophilic) inside the oil surfactant mixture.
3. They will be used for the liquid still as solid dosage forms.
4. They need a lower dose of the drug concerning conventional dosage forms.

Advantages of self-emulsifying drug delivery system over standard drug delivery systems [13]: -

1. Fine oil drops of self-micro emulsifying drug delivery systems would pass rapidly facilitating wide distribution of the drug throughout the stomach and promote the wide distribution of the drug throughout the GI tract.

2. Emulsions are sensitive and metastable dispersed forms, whereas self-micro emulsifying drug delivery systems are physically stable formulations.

3. Compared with oily solutions, they supply a large interfacial area for partitioning the drug between oil and water.

4. Potential advantages of these systems include enhanced oral bioavailability, further consistent temporal profiles of drug absorption, selective drug targeting toward a specific absorption window in the GI tract, and drug protection from the hostile environment within the gut. Thus, for lipophilic drug compounds that show off dissolution charge-restrained absorption, those structures may also provide development in the charge and volume of absorption and purpose in addition to reproducible blood time profiles.

5. Simple manufacture and scale-up are one among the foremost necessary advantages that make self-micro emulsifying drug delivery systems distinctive when compared to different drug delivery systems like solid dispersions, liposome, nanoparticles, etc., as they require elementary and economical manufacturing facilities like a simple mixer with an agitator and volumetric liquid filling equipment for large-scale manufacturing. This explains the interest of the pharmaceutical industry in the self-micro emulsifying drug delivery systems.

Requirements of self-emulsifying drug delivery systems: -

Oral delivery of poorly water-soluble mixture is to pre-dissolve the compound in an appropriate solvent and fill the formulation into capsules. The substantial gain of this technique is that pre dissolving the compound overcomes the preliminary charge-proscribing step of particulate dissolution withinside the aqueous surroundings within side the GI tract.

However, the major problem is that the drug may precipitate out of solution when the formulation disperses in the GI tract, mainly if a hydrophilic solvent is used (e.g., polyethylene glycol). If the drug may be dissolved in a lipid vehicle, there is less potential for precipitation on dilution in the GI tract. A different strategy for poorly soluble drugs is to formulate in a solid solution using a water-soluble polymer to aid the solubility of the drug compound. For example, polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG 6000) prepare solid solutions with poorly soluble drugs. One major problem within this type of formulations is that the drug may favor a further thermodynamically stable state, leading to the compound crystallizing in the polymer matrix. Therefore the physical stability of such formulations needs to be assessed using techniques such as differential staining calorimetric or X-ray crystallography. In this case, the self-emulsifying drug delivery systems are an excellent way to solve this [14, 15, 16].

Disadvantages of SEDDS Systems [13]: -

1. One among the obstacles to the development; of self-micro emulsifying drug delivery systems and different lipid-based formulations is the lack of good predictive *in vitro* models for the assessing the formulations.

2. The Traditional dissolution systems do not work because these formulations potentially are dependent on dissolution before the release of the drug.

3. The disadvantages of this system include chemical instabilities of dosage forms and high surfactant concentrations in formulations (approximately 30-60%) which irritate GIT.

4. Volatile co-solvents in the standard self-micro emulsifying drug delivery systems formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.

5. Formulations containing many components become challenging to validate.

6. High production prices.

7. Low drug incompatibility.

8. Drug leakage. So it possible to allow less amount of drug loading.

Factors affecting SEDDS

1. **Nature and dose of the drug: -** Drugs which are administered at a very high dose are not suitable for self-micro emulsifying drug delivery systems unless they exhibit excellent solubility in at least one of the components of self-micro emulsifying drug delivery systems, preferably the lipophilic phase. The drugs or medicaments with limited solubility in water or aqueous solutions and lipids with log P values of approximately two are most challenging to deliver by self-micro emulsifying drug delivery systems [17]. The ability of self-micro emulsifying drug delivery systems to maintain the drug in solubilized form is greatly influenced by the solubility of the drug in the oil phase.

2. **Concentration of Surfactant or co-surfactant: -** If surfactant; or co-surfactant were contributed to the greater extent in drug solubilization then there would be a risk of precipitation, as dilution of self-micro emulsifying drug delivery systems will be lead to lowering of that solvent capacity of the surfactant or co-surfactant.

3. **Polarity of lipophilic phase: -** The polarities of the lipid phases are one of the very factors that govern the drug release from the microemulsions. The contradictions of the drop are governed by the 'HLB' the chain length and degree of unsaturation of the fatty acid and therefore the molecular weight of the micronized drug.

The Method of Emulsification:-

1. **Mechanism of self emulsification:** Self emulsification occurs when the entropy or energy change occurs**.** The free energy of standard emulsion formation may be direct operation of the power needed to make a brand new surface between the 2 phases and may be delineated by the equation.

$$\Delta G == \Sigma N \pi r^2 \sigma \qquad (i)$$

Where wherever **Δ G** is that the free energy related to the method (ignoring the free energy of mixing), **N** is that the variety of drops of radius **r, σ** is surface energy with time.

The two phases of the emulsion may tend to separate to cut back the surface space and, afterward the free energy of the system. Therefore, the emulsions ensuing from binary compound dilution area unit stabilized by standard emulsifying agents, that type a monolayer around the emulsion drops and thus, cut back the surface energy, also as providing a barrier to coalescence [18]. Inside the case of a self-emulsifying system, the free energy needs to make the emulsion is either low or positive or negative; then the emulsion method happens spontaneously [19].

Emulsification needs little or no input energy, involves destabilization through the contraction of native surface regions. For emulsification to occur, the surface structure should don't have any resistance to surface shearing [20]. Emulsification is related to the benefit by that water penetrates the various liquid crystals or phases that get shaped on the surface of the drop. The addition of a binary mixture (oil/non-ionic surfactant) to the water ends up in the interface formation between the oil and binary compound continuous phases, followed by the solubilization of water among the oil section thanks to binary compound penetration through the interface that happens till the solubilization limit is reached about to the interface [21].

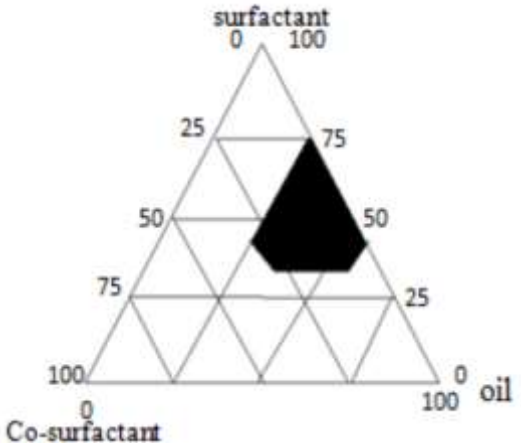
Further, aqueous penetration will cause the formation of the dispersed liquid crystalline phase. As the aqueous penetration proceeds, eventually all materials close to the interface will be a liquid crystal, the real amount depending on the surfactant concentration or amount in the binary mixture or solution once formed, vastly penetration of water into the aqueous chambers or cores, aided by the gentle mixing of the self emulsification process which causes disturbance of interface and drops formation. The high solubility of these self-emulsified systems to coalescence is considered to be due to the liquid crystal interface surrounding the oil drops.

2. Formation of ternary phase diagrams: This is the starting phase of formulation. It is helpful to identify the best emulsification region of oil, surfactant, and co-surfactant combinations. Ternary phase diagram of surfactant, co-surfactant, and oil will plot; each of them representing an apex of the triangle [22]. The strategies area unit accustomed plot ternary section diagrams area unit precisely the Dilution technique and Water volumetric analysis technique area unit shown in figure 3.

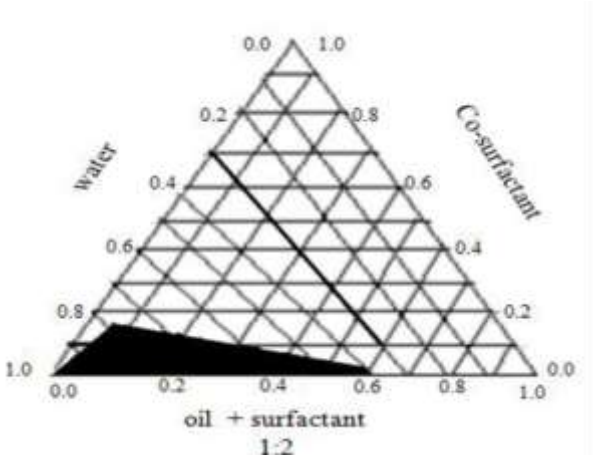
a. ***Dilution method*:** Ternary mixtures with varied compositions of a surface-active agent, co-surfactant, and oil were ready. The share of surface-active agent, co-surfactant, and oil determined supported the necessities. Compositions area unit evaluated for nanoemulsion formation by diluting associate degree applicable quantity of mixtures with applicable double H_2O. The ball size of the ensuing dispersions was firm by victimization chemical analysis (as shown in figure 3a) was known for the various system during which nanoemulsions with need ball size were obtained.

b. ***Water volumetric analysis or titration method:*** The pseudo-ternary part diagrams were furtherly made by volumetric analysis of solid-liquid mixtures of oil, surfactant, and co-surfactant with water temperature (as shown in figure 3b). The oil part, Surfactant, and therefore the co-surfactant, at Km, values 1.5 and one (surfactant: co-surfactant ratio), oily mixtures of oil, surface-active agent [17]. Every mixture was then slowly titrated with aliquots of H_2O and stirred at temperature to realize equilibrium.

The solution was physically examined for transparency. When equilibrium was reached, the mixtures were further titrated with aliquots of H_2O till they showed cloudiness. Clear and isotropous samples were deemed to be among the microemulsion areas. No tries were created to utterly establish the opposite regions of the part diagrams. Supported the results, Associate in Nursing's applicable share of oil, surfactant, and co-surfactant was designated, related inside the part diagram, and were used for the preparation of SMEDDS.



(A) Dilution methodology



(B) Titration methodology

Figure 3: Ternary phase diagram of mechanism of emulsification

Excipients used for self-emulsifying drug delivery systems:-

The self-emulsifying method depends on:

1. The character of the oil–surfactant combines
2. The surface-active agent concentration
3. The temperature at that self-emulsification happens [23].

1. ***Oil:*** Both long and medium-chain triglyceride (MCT) oils with different degrees of saturation are used for the planning of SEDDS. Unqualified edible oils the foremost 'natural' basis for lipoid vehicles however, their poor ability to dissolve massive amounts of hydrophobic medication and therefore their relative issue in economical self emulsification [24, 25]. MCT was most popular inside the earlier SEDDS due to its higher liquidity, higher solubility properties and self emulsification ability, however, apparently, they're thought-about less enticing compared to the novel semi-synthetic medium-chain derivatives, which may be outlined instead as amphiphilic compounds exhibiting surface-active agent properties. Polyethylene glycol (PEG) with mixed carboxylic acid and polythene glycol (PEG) chain lengths giving them a varied hydrophilic-lipophilic balance (HLB) price, together with vegetable oils, are wont to solubilize poorly soluble medication and improve their bioavailability [26].

2**. *Surfactants*:** The non-ionic surfactants having a relatively high hydrophilic and lipophilic balance (HLB) was advised for the design of self dispersion systems, where the various liquid or solid ethoxylated poly glycoiysis glycerides and Tween 80 square measure the foremost often used excipients. Non-ionic surfactants square measure

illustrious to be less cyan genetic compared to active ionic agents, however they will cause moderate reversible changes in enteric wall permeableness. Various nonionic surfactants like the polysorbates and polyols, which cover the HLB range from 2 to 18, could also be utilized in combination with lipid excipients to market self-emulsification or micro-emulsification. Due to their dehydrating effect on the capsule gelatin, there is a tendency for hard and soft gelatin capsules to become brittle at high concentrations. Surfactants have a high HLB & hydrophilic, which assist the immediate formation of O/W drop & rapid spreading of the formation in aqueous media. Surfactants are amphiphilic & they may dissolve or soluble relatively high amount of hydrophobic drug compounds. This may prevent precipitations of the drug inside the GI lumen & for prolong existence of drug molecules [25].

3**. *Co-solvents*:** Organic solvents, appropriate for oral administration (ethanol, propylene glycol (PG), polyethylene glycol etc. could facilitate to dissolve of massive amounts of either the deliquescent surface-active agent or the drug inside the lipoid base [27].

Example: Co-solvents like diethylene glycol monoethyl ether, propylene glycol, polyethylene glycol, polyoxyethylene, *tetra hydrofurfuryl* alcohol, and polyethylene glycol ether etc [28].

4**. *Consistency builder*:** Further materials are often supplemental to change the consistency of the emulsions; such materials are tragacanth, cetyl alcohol, stearic acids, and,or beeswax.

5**. *Polymers*:** Inert chemical compound matrix representing from 5 to 40% of the composition relative to the load, that isn't ionizable at physiological pH and being capable of forming matrix square measure used. Examples are included hydroxypropyl methylcellulose, ethylcellulose, etc [29].

Method of Preparation

Solidifying techniques for transforming liquid/semisolid:-

Various solidifying techniques areas listed below [30]. *Capsule filling with liquid and solid self- emulsifying formulations* Capsule filling is the only and therefore the foremost typical technology for the encapsulation of liquid or solid self- emulsifying formulations for the oral route. For solid formulations, it's a four-step process:-

• Heat the semi-solid filler to at least 20 °C above its melting point.

• Incorporation of the active substances with the assistance of stirring.

• Capsule filling with mild cooling to room temperature. For liquid formulations, it involves two-step ways.

• Filling of the drugs into the capsules at the moment sealing of the body and cap of the capsule, either by micro sprays sealing or banding method.

Spray drying

Essentially, this method involves preparing a formulation by intermixture lipids, surfactants, drugs, solid carriers, and solubilization of the mixture before spray drying. The solubilized liquid formulation is then atomized into a twig of drops.

The drops square measure introduced into a drying chamber, wherever the volatile part (e.g., the water contained in Associate in Nursing emulsion), gaseous and ready into pill pattern therefore the drying chamber style square measure designated in line with the drying characteristics of the merchandise and powder specifications.

Adsorption is done by solid carriers

Free flowing powders are also obtained from liquid self-emulsifying formulations by surface assimilation to solid carriers. The surface assimilation method is easy and simply involves adding the liquid onto pages by mixture in a very mixer.

Melt granulation

Melt granulation could be a method inside which powder agglomeration is obtained through adding a binder that melts or softens at comparatively low temperatures. As a 'one-step' operation, ease granulation offers many benefits compared with typical wet granulation, since the liquid addition and so the following drying part square measure omitted. Further over, it's additionally an honest different to the utilization of solvent thirty-two. Most parameters

that management the granulation method square measure vane speed, mixture time, binder particle size, and so the consistency of the binder. The soften granulation method was sometimes used to absorbing SES (lipids, surfactants, and drugs) onto solid neutral carriers (mainly silicon dioxide and Mg aluminum silicate).

Melt extrusion or extrusion spheronisation

Melt extrusion could be a solvent-free method that permits high drug loading (60%) similarly to content uniformity [31]. Extrusion may be a product of uniform shape and density by forcing it through a die under controlled temperature, product flow, and pressure conditions. this dimensions of the extruder aperture will determine the approximate size of the resulting spheroids. The extrusion–spheronization method is usually employed in the pharmaceutical trade to create uniformly sized spheroids (pellets) [32].

Characteristics of self-emulsifying drug delivery systems (SEDDS)

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

Visual assessment

This may provide necessary information relating to the self-emulsifying and little emulsifying property of the mixture, therefore the following dispersion [33, 34].

Turbidity measurement

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

Drop size

This is a significant take into account self-emulsification performance as a result of it determines the speed and extent of drug unharnessed still as a result of the strength of the emulsion [35,36, 37]. Photon correlation spectroscopy, microscopic techniques, or a Coulter Nanosizer are chiefly used for the determination of the emulsion drop size [38, 39, 40]. The reduction of the drop size to values below 50 μm leads to the formation of self-micro emulsifying drug delivery systems, which are stable, isotropic, and precise o/w dispersions [41].

Zeta potential measurement

This is wont to establish the charge of the drops. In conventional SEDDSs, the charge on associate oil drop is negative due to the presence of free fatty acids [42].

Find out emulsification time

Self-emulsification time, dispersibility, look and flow ability were determined and scored [43].

Future Trend

In respect to the formulation development of poorly soluble medication inside the future (Table 1), there proper measure presently techniques getting used to convert liquid or semisolid self-emulsifying drug delivery systems and self-micro emulsifying drug delivery systems formulations into powders and granules, which may then be further processed into typical capsules or may be compressed into tablets. Hot soften granulation may be a technique for manufacturing granules or pellets and, by employing a waxy solubilizing agent as a binding agent, up to 25% solubilizing agent are often incorporated during a formulation.

There is further increasing interest in exploitation inert adsorbents, like the Neusilin merchandise, for changing liquids into powders which may then be processed into powder fill capsules or tablets. Oral delivery of poorly water-soluble compounds is to pre dissolve the compound during an appropriate solvent and fills the formulation into capsules.

The main advantage of this approach is that pre dissolving the compound overcomes the initial rate-limiting step of particulate dissolution inside the binary compound surroundings among the lowlife. However, a possible disadvantage is that the drug could precipitate out of the answer once the formulation disperses inside the GIT.

Table 1: Marketed SEDDS Formulation [44, 45, 46].

Brand name	Drug used	Dosage form	Company
Neoral	Cyclosporine	SGC	Novartis
Norvir	Ritonavir	SGC	Abott laboraties
Fortovase	Saquinavir	SGC	Hoffmann roche
Agenerase	Amprenavir	SGC	GSK
Convulex	Volporic acid	SGC	Pharmacia

Application of Self Emulsifying Drug Delivery System (SEDDS)

Supernatural self-emulsifying drug delivery system (S-SEDDS)

The high surface-active agent level generally gift in SEDDS formulations will lead to GI aspect effects and a replacement category of supersaturate formulations, as well as supersaturate SEDDS (S-SEDDS) formulations, are designed and developed to scale back the surface-active agent aspect effects and accomplish fast absorption of poorly soluble drugs [47,48,49,50,51]. The S-SEDDS approach is intended to get a long saturated answer of the drug once the type granulation are free from associate in administering appropriate indefinite quantity form into associate in a administer binary compound medium. Supersaturating is meant to extend the physical science activity of the drug on the far side its solubility limit and, therefore, to end in associate in delivering hyperbolic propulsion for transit into and across the biological barrier [52] e.g., drug moiety in administration S-SEDDS of paclitaxel (PTX) was developed exploitation hydroxypropyl alkyl group polysaccharide (HPMC) as a precipitation matter with a standard SEDDS formulation, and a poorly soluble drug, PNU-91325, was developed as associate in delivering S-SEDDS. It's price accentuation that the considerably reduced quantity of surface-active agent utilized in the S-SEDDS formulation approach provides an improved toxicity or safety profile than the standard SEDDS formulations [53, 54].

Self-emulsifying solid drug delivery system (SEDDS)

SEDDS are normally prepared as liquid dosage forms that may be administrated in soft gelatine capsules, which have some disadvantages, especially in the manufacturing process. An alternative method is the incorporation of liquid self-emulsifying ingredients into a powder to create a solid dosage form (tablets, capsules). A pellet formulation of progestin in SEDDS has been ready by the method of extrusion/spheronization to supply a decent in vitro drug release (100% among half-hour, T50% at thirteen minutes) [55, 56].

Current Approaches in Self emulsifying Drug Delivery System (SEDDS)

1. SEDDS of coenzyme Q10 was prepared and this resulted in increased bioavailability and reduced toxicity [57].
2. Lipophilic compound WIN 54954 was developed as SEDDS in triglyceride oil/nonionic surface-active agent mixtures. It resulted in improved plasma profile in terms of Cmax and Tmax [58].
3. Self-micro emulsifying drug delivery system and self-micro emulsifying drug delivery systems of simvastatin were developed to enhance their oral bioavailability. This study was focused on the potential use of self-micro emulsifying drug delivery systems for the delivery of hydrophobic compounds [59].
4. Produced a new PTX-SEDDS (for the treatment of solid tumors), and it was found that SEDDS was chemically and physically stable for one year when kept as a two-part formulation and also the drug loading for the formulation was increased by approximately fivefold. Compared to marketed i.v. formulation products, the excipients were presented a significantly reduced cytotoxicity, and led to a stable microemulsion [60].
5. An antimalarial drugs eg., Halofantrine, were prepared as self-emulsifying drug delivery systems and self-micro-emulsifying drug delivery systems and resulted in an eight times improvement in absolute oral bioavailability relative to previous clinical data of the solid [61].
6. Increased bioavailability of up to 1.88 silymarin was achieved by self-micro emulsifying drug delivery systems [62].

7. Using a self-emulsifying drug delivery system, a self nano emulsified drug delivery system of ubiquinone was prepared, therefore the study shows that self-nano emulsifying drug delivery systems overcame the disadvantages of the traditional emulsified system, such as low solubility, and irreversible precipitation of the active drug in the vehicle within time [63].
8. The two novel SMEDDSs containing Labrasol with completely different dilutions on tight junction were studied and located that Labrasol at a level of o.1 % and 1.0 % was shown to extend the permeability of Osmitrol by 4.6-fold and 33.8-fold, respectively [64].
9. The solid self-emulsifying systems were used in the delivery of diclofenac and results showed that diclofenac could be comfortably administered in the form of self-emulsifying tablets using goat fat, and tween 65 admixtures [65].
10. Self-emulsifying drug delivery systems containing ketoprofen were developed as sustained and controlled release dosage form, and it was found that the release patterns of drugs were improved [66].
Some of the marketed drugs' dosages from products are summarized in table 2 [67].

Table 2: Enlisted Market products

Brand name	Drug	Dose	Dosage form
PaninumBioral®	Cyclosporine	50mg,100mg	Soft gelatin capsule
Lipirex®	Fenofibrate	10mg	Hard gelatin capsule
L-Ors Soft Captm Alza®	Guaiphenesin	200 mg	Osmotic pump
Convulex®	Valproic acid	150,300,500 mg	Soft gelatin capsule
JuvelaN®	Tocopherol nicotinate	200 mg	Soft gelatin capsule
Agenerase®	Amprenavir	50 mg	Soft gelatin capsule
Rapamune®	Sirolimus	0.5,1,2 mg	Oral solution
Targretin/ Bexarotene®	Bexarotene	75 mg	Soft gelatin capsule
Gengraf®	Cyclosporin A	25,100 mg	Hard gelatin capsule
Zipsor®.	Diclofenac potassium.	25 mg	Soft gelatin capsule
Kaletra®	Lopinavir, Ritonavir	20,80 mg/ml	Oral solution
Fortovase®	Saquinavir	200 mg	Soft gelatin capsule
Aptivus®.	Tipranavir.	250 mg.	Soft gelatin capsule.
Accutane®	Isotretinoin	10,20,40 mg	Soft gelatin capsule
Sandimmune®	Cyclosporin	25,50,100 mg	Soft gelatin capsule
Solufen®.	Ibuprofen.	-	Hard gelatin capsule.
Neoral®	Cyclosporin	25,100 mg	Soft gelatin capsule and Oral solution
Depakene®	Valproic acid	250,500 mg	Soft gelatin capsule
Vesanoid®.	Tretinoin.	10 mg.	Soft gelatin capsule.
Norvir®	Ritonavir	80mg/ml	Oral solution
Rocatrol®	Calcitriol	0.25,0.5 µg	Soft gelatin capsule

Authors Contributions or Conflict of Interest

The contributions of all authors are the same. The author confirms that there is no conflict of interest, financial or different wise.

References

[1]. Burcham DL, Maurin MB, Hausner EA, Huang SM. The improved oral bioavailability of the hypocholesterolemic DMP 565 in dogs following oral dosing in oil and glycol solutions. Biopharm Drug Dispos. 1997; 18: 737-42.
[2]. Groves MJ, Mustafa RMA, Carless JE. Phase studies of mixed phosphate surfactants, n-hexane, and water. J Pharm Pharmacol. 1947; 26: 616-23.

[3]. Pouton CW, Wakerly MG, Meakin BJ. Self-emulsifying systems for oral delivery of drugs. Proc Int Symp Control Releases Bioact Mater. 1987; 14: 113-4.
[4]. Craig DQ. The use of self-emulsifying systems as a means of improving drug delivery. BT Gattefosse 1993; 86:21-31.
[5]. Pouton CW. Self-emulsifying drug delivery systems: Assessment of the efficiency of emulsification. Int J Pharm. 1985; 27: 335-48.
[6]. Garrigue JS, Lambert G, Benita S. Self-emulsifying oral lipid-based formulations for improved delivery of lipophilic drugs. In: Drugs and therefore the Pharmaceutical Sciences. Microencapsulation Methods and Industrial Applications. 2nd ed. Chap. 13. Benita S, editor. Switzerland: Informa Healthcare; 2005. p. 429-80.
[7]. Craig DQ, Lievens HS, Pitt KG, Storey DE. An investigation into the physicochemical properties of self-emulsifying systems using low-frequency dielectric spectroscopy, surface tension measurements and particle size analysis. Int J Pharm 1993; 96: 147-55.
[8]. Mistry R, Sheth N S: Self-emulsifying drug delivery system. International Journal of Pharmacy and Pharmaceutical Sciences. 2011; 3(2): 23-28.
[9]. Choukseyr, *et al*: Preparation and evaluation of the self-emulsifying drug delivery system containing atorvastatin HMGCOA inhibiter. International Journal of Pharmacy and Pharmaceutical Sciences. 2011; 3(3): 147-152.
[10]. Shukla J B, *et al*: Self micro emulsifying drug delivery system pharma science monitor. Journal of Pharmacy and Pharmaceutical Sciences. 2010; 1(2): 13-33.
[11]. Pouton CW. Self emulsified drug delivery systems: assessment of the efficiency of emulsification. Int J Pharm. 1985; 27: 335-48.
[12]. Sapraa K, *et al*: Self Emulsifying Drug Delivery System: A Tool in Solubility Enhancement of Poorly Soluble Drugs; Indo Global Journal of Pharmaceutical Sciences 2012; 2(3): 313-332.
[13]. Shukla J B, *et al*: Self micro emulsifying drug delivery system pharma science monitor. Journal of Pharmacy and Pharmaceutical Sciences. 2010; 1(2): 13-33.
[14]. Reiss H. Entropy induced dispersion of bulk liquids. J Colloid Interface Sci. 1975; 53: 61–70.
[15]. Constantinides PP. Lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects. Pharm Res. 1995; 12: 1561–72.
[16]. Dabros T, Yeung A, Masliyah J, Czarnecki J. Emulsification through area contraction. J Colloids Interface Sci. 1999; 21: 222–4.
[17]. Sharma V, *et al*: SELF-MICRO EMULSIFYING DRUG DELIVERY SYSTEMS: A novel approach for lipophilic drugs. International Journal of Pharmaceutical Science and Research 2012; 3(8): 2441-2450.
[18]. BhargavaP, Bhargava S, and Daharwal S J: Self-emulsifying drug delivery System: an approach to improve the solubility of poorly water soluble drugs. Advance Research in Pharmaceuticals and Biologicals. 2011; 1(1): 1-9.
[19]. Christopher Porter J H, *et al*: Enhancing intestinal drug solubilization using lipid-based delivery systems. Advanced Drug Delivery Reviews. 2008; 60: 673–691.
[20]. Kumar A, Sharma S, Kamble R: Self-emulsifying drug delivery system (SEDDS): future aspects. International Journal of Pharmacy and Pharmaceutical Sciences. 2010; 2(4): 7-13.
[21]. Mittal P, Seth N, Rana AC: Self-micro emulsifying drug delivery system (SELF-MICRO EMULSIFYING DRUG DELIVERY SYSTEMS): An alternative approach for hydrophobic drugs. International Journal of Natural Product Science. 2012; 1: 80.
[22]. Sudheer P, *et al*: Approaches to the development of solid- self micron emulsifying drug delivery system: formulation techniques and dosage forms – a review. Asian Journal of Pharmacy and Life Science. 2012; 2(2): 214-225.

[23]. Sugimoto M, Okagaki T, Narisawa S, Koida Y, Nakajima K. Improvement of dissolution characteristics and bioavailability of poorly water-soluble drugs by novel co-grinding method using water-soluble polymer. Int J Pharma 1998; 160: 11-9.
[24]. Gershanik T, Benita S. Self-dispersing lipid formulations for improving oral absorption of lipophilic drugs: Euro J Pharm Biopharm. 2000; 50: 179-88.
[25]. Rajan B, Nirav S. A review: Self emulsifying drug delivery system. Int J Pharm Pharm Sci. 2011; 3(2): 23-28.
[26]. Tang JL, Sun J, He ZG. Self- Emulsifying Drug Delivery Systems: Strategy for Improving Oral Delivery of Poorly Soluble Drugs. Curr Drug Therapy. 2007; 2: 85-93.
[27]. Wakerly MG, Pouton CW, Meakin BJ, Morton FS. Self emulsification of vegetable oil-nonionic surfactant mixtures: ACS Symp Ser. 1986; 311: 242-55.
[28]. Dey P, Maiti S, Ray S, Sa B, Sen K. Self-Emulsification of Poorly Soluble and Highly Permeable Drugs: An Overview Int J Pharma Recent Res. 2009; 1(1): 67-72.
[29]. Roop NG, Rakesh G, Singh RG. Enhancement of oral bioavailability of lipophilic drugs from self micro emulsifying drug delivery system (self-micro emulsifying drug delivery systems). Int J Drug Dev & Res. 2009 sep-dec; 1(1):10-18.
[30]. Khoo S, Humberstone AJ, Porter CJ, Edwards GA, Charman WN. Formulation design and bioavailability assessment of lipidic self-emulsifying formulations of halofantrine. Int J Pharm 1998; 167: 155-64.
[31]. Hauss DJ, Fogal SE, Ficorilli JV, Price CA, Roy T, Jayaraj AA, *et al*. Lipid-based delivery systems for improving the bioavailability and lymphatic transport of poorly water-soluble LTB4 inhibitor. J Pharm Sci. 1998; 87: 164-9.
[32]. Kumar A, Sharma S, Kamble R. Self emulsifying drug delivery system (SEDDS): Future aspects. Int J Pharm Pharm Sci. 2010; 2(4):7-13.
[33]. Holm R, Jensen IH, Sonnergaard J. Optimization of self-micro emulsifying drug delivery system using D-optimal design and therefore the desirability function. Drug Dev Ind Pharm. 2006; 32: 1025-32.
[34]. Shen H, Zhong M. Preparation and evaluation of self-micro emulsifying drug delivery system containing atorvastatin. J Pharm Pharmacol. 2008; 58: 1183-91.
[35]. Patil P, Joshi P, Paradkar A. Effect of formulation variables on preparation and evaluation of gelled self-emulsifying drug delivery systems of ketoprofen. AAPS Pharm Sci Tech 2004; 5: 1-8.
[36]. Shen HR, Zhong MK. Preparation and evaluation of self micro emulsifying drug delivery systems containing atorvastatin. J Pharm Pharmacol. 2006; 58: 1183-91.
[37]. Wei L, Sun P, Nie S, Pan W. Preparation and evaluation of SEDDS and SELF-MICRO EMULSIFYING DRUG DELIVERY SYSTEMS containing Carvedilol. Drug Dev Ind Pharm. 2005; 31:785-94.
[38]. Kang BK, Lee JS, Chon SK, Jeong SY, Yuk SH, Khang G, *et al*. Development of self-micro emulsifying drug delivery systems for oral bioavailability enhancement of simvastatin in the beagle dog. Int J Pharm 2004; 274: 65-73.
[39]. Hong JY, Kim JK, Song YK, Park JS, Kim CK. A new self-emulsifying formulation of itraconazole with improved dissolution and oral absorption. J Control Release. 2006; 110: 332-8.
[40]. Chae GS, Lee JS, Kim SH, Seo KS, Kim MS, Lee HB, *et al*. Enhancement of the stability of BCNU using self-emulsifying drug delivery systems (SEDDS) and *in vitro* antitumor activity of self-emulsified BCNU-loaded PLGA wafer. Int J Pharm. 2008; 301: 6-14.
[41]. Kommuru TR, Gurley B, Khan MA, Reddy IK. Self-emulsifying drug delivery systems (SEDDS) of coenzyme Q10: Formulation development and bioavailability assessment. Int J Pharm. 2005; 212: 233-46.
[42]. Attama AA, Nzekwe IT, Nnamani PO, Adikwu MU, Onugu CO. The use of solid self-emulsifying systems in the delivery of diclofenac. Int J Pharm 2003; 262:23-8.
[43]. Serratoni M, Newton M, Booth S, Clarke A. Controlled drug release from pellets containing water-insoluble drugs dissolved in a self-emulsifying system. Eur J Pharm Biopharm. 2007; 65: 94-8.

[44]. Tang B, Cheng G, Gu JC, Xu CH. Development of solid self-emulsifying drug delivery systems: Preparation techniques and dosage forms. Drug Discov Today. 2008; 13: 606-12.
[45]. Jannin V, Musakhanian J, Marchaud D. Approaches for the development of solid and semi-solid lipid-based formulations. Adv Drug Deliv Rev. 2008; 60: 734-46.
[46]. Yin YM, Cui FD, Mu CF, Choi MK, Kim JS, Chung SJ, *et al*. Docetaxel microemulsion for enhanced oral bioavailability: Preparation and *in vitro* and *in vivo* evaluation. J Control Release. 2009; 140: 86-94.
[47]. Amidon GL, Lennernas H, Shah VP, Crison JR. Theoretical basis for a biopharmaceutical classification: The correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharm Res. 1995; 12: 413-20.
[48]. Franceschinis E, Voinovich D, Grassi M, Perissutti B, Filipovic-Grcic J, Martinac A, *et al*. self-emulsifying pellets prepared by wet granulation in high shear mixer: Influence of formulation variables and preliminary study on the *in vitro* absorption. Int J Pharm 2005; 291: 87-97.
[49]. Newton M, Petersson J, Podczeck F, Clarke A, Booth S. The influence of formulation variables on the properties of pellets containing a self-emulsifying mixture. J Pharm Sci 2000; 90: 987-95.
[50]. Reiss H. Entropy-induced dispersion of bulk liquid. J Colloid Interface Sci 1975; 53: 61-70.
[51]. Groves MJ, Mustafa RM. Measurement of "spontaneity" of self emulsifiable oils. J Pharm Pharmacol 1974; 26: 671-88.
[52]. Groves MJ, Mustafa RM, Carless JE. Phase studies of mixed surfactants n-hexane and water. J Pharm Pharmacol 1974; 26: 616-23.
[53]. Friedman D. Non-aqueous compositions for oral delivery of insoluble bioactive agents. US Patent.
[54]. Ockner RK, Manning JM. Fatty acid-binding protein in the small intestine; identification, isolation, and evidence for its role in cellular fatty acid transport. J Clin Invest. 1974; 54: 326-38.
[55]. Greenberger NJ, Rodgers JB, Isselbacher KJ. Absorption of medium and long-chain triglycerides: Factors influencing their hydrolysis and transport. J Clin Invest. 1966; 45: 217-27.
[56]. Porter CJ, Charman WN. Uptake of a drug into the intestinal lymphatic after oral administration. Adv Drug Deliv Rev. 1997; 25: 71-89.
[57]. Cheema M, Palin K, Davis SS. Lipid Vehicles for intestinal lymphatic drug transport. J Pharm Pharmacol. 1987; 39: 55-6.
[58]. Embleton JK, Pouton CW. Structure and function of gastrointestinal lipase. Adv Drug Deliv Rev. 1997; 25: 15-32.
[59]. Wakerley MG, Pouton CW, Meakin BJ, Morton FS. Self-emulsification of vegetable surfactant mixtures: A proposed mechanism of action. Amerimay Chem Soc Symp Ser. 1986; 311: 242-55..
[60]. Ishida M, Tawa R, Shibata N, Takada K. Oral solid gentamicin preparation using emulsifier and adsorbent. J Control Release. 2005; 105: 23-31.
[61]. Nazzal S, Khan MA. Controlled release of a self-emulsifying formulation from a tablet dosage form: Stability assessment and optimization of some processing parameters. Int J Pharm. 2006; 315: 110-21.
[62]. Verreck G, Brewster ME. Melt extrusion-based dosage forms: Excipients and processing conditions for pharmaceutical formulations. J. melt extrusion. 2004; 97: 85-95.
[63]. Bamba J, Cave G, Bensouda Y, Tchoreloff P, Pulsieux F, Couarrraze G. Cryoprotection of emulsions in freeze-drying: Freezing process analysis. Drug Dev Ind Pharm 1995; 21: 1749-60.
[64]. Christensen KL, Pedersen GP, Kristensen HG. Technical optimization of redispersible dry emulsions. Int J Pharm. 2001; 212: 195-202.
[65]. Hansen T, Holm P, Schultz K. Process characteristics and compaction of spray dried emulsions containing a drug dissolved in lipid. Int J Pharm. 2004; 287: 55-66.
[66]. Jang DJ, Jeong EJ, Lee HM, Kim BC, Lim SJ, Kim CK. Improvement of bioavailability and photostability of amlodipine using redispersible dry emulsion. Eur J Pharm Sci. 2006; 28: 405-11.
[67]. Kale, A., A., Patravale, V.B. Design and Evaluation of Self-Emulsifying Drug Delivery Systems (SEDDS) of Nimodipine. AAPS Pharm.Sci.Tech. 2008, 9(1), 191–6.