EXPERT OPINION

Potentials and challenges in self-nanoemulsifying drug delivery systems

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Introduction: A significant number of new chemical entities (almost 40%), that are outcome of contemporary drug discovery programs, have a potential therapeutic promise for patient, as they are highly potent but poorly water soluble resulting in reduced oral bioavailability. Self-nanoemulsifying drug delivery systems (SNEDDS) have emerged as a vital strategy to formulate these poorly soluble compounds for bioavailability enhancement.

Areas covered: The review gives an insight about potential of SNEDDS with regards to oral drug delivery. The effect of various key constituents on formulation of SNEDDS and their applications in oral drug delivery is also discussed. Various aspects of formulation, characterization and biopharmaceutical aspects of SNEDDS are also been explored. The choice and selection of excipients for development of SNEDDS is also discussed.

Expert opinion: The ability of SNEDDS to present the drug in single unit dosage form either as soft or hard gelatin capsule with enhanced solubility maintaining the uniformity of dose is unique. With the ease of large-scale production, high drug-loading capacity, improvement in release behavior of poorly water-soluble drugs and improvement of oral bioavailability, SNEDDS have emerged as preferable system for the formulation of drug compounds with bioavailability problems due to poor aqueous solubility.

Keywords: bioavailability, lipid-based systems, oral delivery, poorly soluble drugs, self-emulsifying

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1. Introduction

Almost 50% of the new drugs discovered recently have poor solubility problem and most of them encounter poor bioavailability problem when formulated as oral dosage form [1,2]. The poor water solubility of the drug leads to poor bioavailability with wide inter- and intra-subject variations, presenting the formulation scientists challenge to formulate them as oral dosage form. These poorly soluble molecules can be classified according to the Biopharmaceutics Classification System (BCS) either as class II or class IV. According to BCS classification, class I drugs are highly soluble and highly permeable. BCS class II and class IV drugs are poorly soluble compounds while class III drugs have permeability issues associated with them. To overcome the poor aqueous solubility problem, many approaches have been exploited such as, particle size reduction, complexation with cyclodextrins, salt formation, solid dispersions, use of surfactant, nanoparticles, etc. [3-9]. The advantages and disadvantages with these systems are well known and available in number of reviews. However, lipid-based formulations have a great potential to improve oral bioavailability of poor water-soluble drugs by presenting the drug in a solubilized state in colloidal dispersion. Incorporating the lipophilic drug into inert lipid

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Article highlights.

- Objective of lipid formulation classification system is to identify the most suitable formulation system for specific drugs based on their physicochemical properties and the same for the excipients.
- Self-nanoemulsifying drug delivery systems (SNEDDS) offer more drug-loading capacity when compared with lipids solution.
- Safety and regulatory status (generally regarded as safe status (GRAS)) of the surfactant being used are important factors in the formulation of SNEDDS.
- The choice of the oil phase is often a compromise between ability of oil to solubilize the drug and its ability to facilitate formation of nanoemulsion with desired characteristics.
- Surfactants with high hydrophilic–lipophilic balance (HLB) and high hydrophilicity assist in formation of small oil-in-water (o/w) droplets and rapid spreading of formulation in aqueous media.
- Self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion.
- Droplet size is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release, as well as the stability of the emulsion.

This box summarizes key points contained in the article.

vehicle such as oils (tri-, di- and monoglycerides), surfactant, liposomes, self-nanoemulsifying drug delivery systems (SNEDDS) can improve the poor bioavailability problem associated with lipophilic drugs. The present review describes how SNEDDS can be used as a strategy to improve bioavailability of poorly water-soluble drugs. Various methods of characterization and biopharmaceutical aspects of SNEDDS have been discussed. The authors have tried to explain the effect of the key constituents for the formulation of SNEDDS. The selection criteria of different components and the application of SNEDDS in oral drug delivery are also discussed.

SNEDDS are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or alternatively, one or more hydrophilic solvents and co-solvents/surfactants that have a unique ability of forming fine oil-in-water (o/w) emulsions on mild agitation followed by dilution in aqueous media, such as gastrointestinal (GI) fluids [10]. SEDDS are mixtures of oils and surfactants, ideally isotropic, and sometimes containing co-solvents, which emulsify spontaneously to produce fine o/w emulsions when introduced into aqueous phase under gentle agitation [11].

These lipid-based systems as opposed to the polymeric system are easily taken up by the body. The digestion of these formulations involve dispersion of fat globules into a coarse emulsion of high surface area, enzymatic hydrolysis of fatty acid glyceryl esters (primarily triglyceride lipid) at the oil/water interface and dispersion of the products of lipid digestion into an absorbable form. The resemblance of their degradation product with end product of intestinal degradation has contributed in their wide acceptance for SNEDDS.

2. Lipid formulation classification system

Pouton [12] and Pouton and Porter [13] introduced the lipid formulation classification in 2000 in order to identify the factors affecting the *in vivo* behavior of formulation. One of the main objectives of this classification system is to identify the most suitable formulation system for specific drugs based on their physicochemical properties and the same for the excipients. **Table 1** briefly describes the characteristics of different systems.

2.1 Type I

Type I systems consist of formulations which comprise drug in solution in triglycerides and/or mixed glycerides. Typically, lipophilic materials are blends of food glycerides derived from vegetable oils, which are safe for oral ingestion, rapidly digested and absorbed completely from the intestine. Because type I systems do not contain surfactant, these systems exhibit poor initial aqueous dispersion and have very limited ability to self-disperse in water. They depend on digestion by pancreatic lipase/co-lipase in the GI tract to generate more amphiphilic lipid digestion products and promote drug transfer into the colloidal aqueous phase. Theses system are suitable for highly lipophilic drugs (logP > 4), where drug solubility in oil is sufficient to allow incorporation of the required dose. The advantage of type I system lies in the generally regarded as safe status (GRAS) of excipients, simplicity and their compatibility with capsules.

2.2 Type II

Type II lipid formulations (typically referred to as SEDDS) are isotropic mixtures of lipids and lipophilic surfactants (hydrophilic–lipophilic balance (HLB) < 12) that self-emulsify to form fine o/w emulsions when introduced in aqueous media. Self-emulsifying systems are formed when the surfactant concentration exceeds 25%w/w, the optimum concentration range being 30 – 40% surfactant. Above 50% surfactant, these systems emulsify slowly due to the formation of viscous liquid crystalline phases at the oil/water interface. Poorly soluble drugs can be dissolved in these systems and encapsulated in hard or soft gelatin capsules to produce convenient single unit dosage forms. Type II lipid-based formulations generate large interfacial areas which in turn allows efficient partitioning of drug between the oil droplets and the aqueous phase from where absorption occurs. An advantage of type II formulations is that they are unlikely to lose solvent capacity on dispersion.

2.3 Type III

Type III lipid-based formulations are defined by the inclusion of hydrophilic surfactants (HLB > 12) and co-solvents such as ethanol, propylene glycol (PG) and polyethylene glycol

Table 1. Lipid formulation classification system and their characteristics.

Type I	Type II	Type III A	Type III B	Type IV
No surfactant	Surfactant (moderate HLB)	Surfactant (higher HLB)	Surfactant and co-solvent	High concentration of surfactant and co-solvent
Poor self-dispersion Digestion required	Self-dispersing Will be digested	Self-dispersing May function without digestion	Transparent dispersion May function without digestion	Micelle or mixed micelle Thought to be limited digestion

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HLB: Hydrophilic–lipophilic balance.

(PEG). These have the potential to disperse quickly to form fine submicron dispersions, often fine enough to form transparent dispersions. Type III formulations can be further segregated (somewhat arbitrarily) into type IIIA and type IIIB formulations in order to identify more hydrophilic systems (type IIIB), where the content of hydrophilic surfactants and co-solvents increases and the lipid content reduces. Type IIIB formulations typically achieve greater dispersion rates when compared with type IIIA, although the risk of drug precipitation on dispersion of the formulation is higher given the lower lipid content. The best-known example of a successfully marketed type III is the Neoral cyclosporin formulation. In contrast to the earlier Sandimmune cyclosporin formulation (comprising corn oil, polyoxyethylated glycerides (labrafil M-2125-CS) and ethanol) which formed a coarse emulsion on dispersion into water, Neoral spontaneously forms a transparent and thermodynamically stable dispersion with a droplet size below 100 nm when introduced into an aqueous media. These systems mix with water easily and take up so much water that penetration of water into the formulation and subsequent dispersion proceeds rapidly.

2.4 Type IV

Type IV systems are essentially pure surfactants or mixtures of surfactants and co-solvents, do not contain natural lipids and represent the most hydrophilic formulations. These formulations commonly offer increased drug-loading capacity (due to higher drug solubility in the surfactants and co-solvents) when compared with formulations containing simple glyceride lipids and also produce very fine dispersions when introduced in aqueous media. The blending of water-soluble surfactants with co-solvents aids the dispersion of surfactant and reduces the loss of solvent capacity. An example of a type IV formulation is the current capsule formulation of the HIV protease inhibitor amprenavir (Agenerase) which contains TPGS (tocopheryl polyethylene glycol succinate) as a surfactant and PEG 400 and PG as co-solvents.

3. Advantages of SNEDDS over micro/nanoemulsions

SNEDDS have a unique ability of forming fine o/w emulsions on mild agitation followed by dilution in aqueous media, such as GI fluids. As the drug is pre-dissolved in a suitable solvent, the initial rate-limiting step of particulate dissolution in the aqueous environment within the GI tract is overcome by SNEDDS. The ability of SNEDDS to present the drug in single unit dosage form with enhanced solubility maintaining dose uniformity is unique.

SNEDDS offers a number of advantages over the conventional micro/nanoemulsion systems. According to Graves *et al.* [14]., nanoemulsions are metastable dispersions of submicrometer droplets that have a significant surface tension, which form only when extreme shear is applied to fragment droplets strongly and are kinetically inhibited against recombining by repulsive interfacial stabilization due to the surfactant. SNEDDS on the other hand are preconcentrates that on mild agitation followed by dilution in aqueous media, form fine o/w emulsions, typically with droplet sizes between 20 and 200 nm.

3.1 Stability

As these systems do not contain water, they improve the physical and/or chemical stability on long-term storage as compared with nanoemulsions that contain considerable amount of water. Mahmoud *et al.* [15]. prepared self-nanoemulsifying tablets of carvedilol and showed successful incorporation of carvedilol within the SNEDDS, which also improved its stability on dilution with aqueous media in the presence of cellulosic polymers.

3.2 Patient compliance

Most of the SNEDDS formulation comes as capsule/tablet dosage form, the dose is maintained and these show more patient compliance [16-18].

3.3 Palatability

As these formulations can be filled into capsules, no palatability issues are there compared with other liquid formulations.

3.4 Drug loading

Since the solubility of compounds with intermediate partition coefficient (logP 1 – 3) are low in natural lipids compared with amphiphilic surfactants/co-surfactants, SNEDDS offers more drug-loading capacity when compared with lipids solution owing to high concentration of surfactant and co-surfactants and less of oil. Thomas *et al.* [19]. found that

SNEDDS formulated with medium-chain (MC) lipids could dissolve more drug compared with those formulated using long-chain (LC) lipids containing Cremophor® RH40 as surfactant. The high drug-loading capacity is also a key factor in success of commercial products like Fortovase®, which contain 200 mg of drug per capsule.

3.5 Effect of food

SNEDDS have little or no effect on absorption of drug when administered with diet. The lipophilic contents of fatty diet aid in absorption of these systems. In a study conducted on minipigs, Nielsen *et al*. [20]. found that bioavailability of probucol was not affected by fed and fasted state in minipigs when administered as SNEDDS, whereas powder formulation showed considerable variation in fed and fasted state bioavailability. Similarly, Grove *et al*. [21]. found that bioavailability of seocalcitol in minipigs from PG solution was affected by the presence of food, whereas the bioavailability from the lipid-based formulations was less affected by the presence of food. Woo *et al*. [22]. observed that food had a marked effect on absorption of itraconazole from the marketed formulation (Sporanox capsule), whereas the influence was less pronounced for the self-emulsifying formulation of itraconazole (ITRA-GSMP capsule) in human volunteers.

3.6 Quick onset of action

Quick onset of action is required in many conditions, such as inflammation, hypertension and angina. SNEDDS have the ability to facilitate oral absorption of the drug, which results in quick onset of action. Taha *et al*. [23]. found that the t_{max} (an indirect measure of quick onset of action) is reduced and bioavailability is increased when vitamin A is given as SNEDD capsule and SNEDD tablet compared with vitamin A oily solution-filled capsules without any additives. Many other studies also reflect the potential of SNEDDS to increase the bioavailability of drug.

3.7 Ease of manufacture and scale-up

The success of any drug delivery system lies in its industrial applicability. Ease of manufacture and scale-up are key parameters that govern success of industrialization. As SNEDDS require very simple and economical manufacturing facilities, such as simple mixer with an agitator and volumetric liquid filling equipment, they can be easily manufactured at large-scale and offer economical benefits as well.

4. Formulation of SNEDDS

A number of factors needed to be considered before the formulation of SNEDDS. These include the nature and concentration of oily phase, surfactant and co-surfactant or solubilizer, the ratio of the components, especially oil-to-surfactant ratio, physicochemical properties of the drug, such as hydrophilicity/lipophilicity, pK_a, polarity, etc. Silva *et al*. [24]. found that small particle size and polarity of resulting oil droplets are two main factors that determine the efficient release of the drug compounds from these systems. In addition, the safety and regulatory status GRAS of the surfactant being used are important factors in the formulation of SNEDDS. **Table 2** provides a brief account of marketed formulations formulated as self-emulsifying system.

4.1 Drug molecule

Drug lipophilicity and dose of drug are the main criteria that need to be considered before development of SNEDDS. Drug molecules with a logP value of greater than 4 are desirable candidate for such system. Dose of drug should be soluble in small quantity of oil so that it can be easily emulsified on dilution by GI tract fluids when ingested. If higher quantities of oil are required for solubilization of drug, it may lead to a formulation that can't be filled in single dosage unit.

Charman *et al*. [25]. proposed that drug candidates for lymphatic transport should have a logP > 5 and, in addition, a triglyceride solubility > 50 mg/ml. The importance of lipid solubility was illustrated by comparing the lymphatic transport of dichlorodiphenyltrichloroethane (DDT, logP 6.19) with hexachlorobenzene (HCB, logP 6.53). While both compounds have similar logP values, the difference in lymphatic transport on administration in oleic acid, 33.5% of the dose in the case of DDT and 2.3% with HCB, was attributed to the 13-fold difference in triglyceride solubility. However, combination of a high logP and high triglyceride solubility does not always guarantee significant lymphatic transport. Penclomedine, an experimental cytotoxic agent with a logP of 5.48 and a triglyceride solubility of 175 mg/ml, was poorly transported in the intestinal lymph, ~ 3% of the dose [26].

4.2 Oils

The choice of the oily phase is often a compromise between ability of oil to solubilize the drug and its ability to facilitate formation of nanoemulsion with desired characteristics. Unmodified edible oils provide the most natural basis for lipid vehicles, but are not frequently preferred in the formulation of self-emulsifying formulations due to their poor ability to dissolve large amounts of lipophilic drugs [27,28]. Modified LC and MC triglyceride oils, with varying degrees of saturation or hydrolysis have contributed widely to the success of SNEDDS and are accepted for the design of self-emulsifying formulations as they offer formulative and physiological advantages. Their ability to form good emulsification system with most of surfactant having GRAS status and resemblance of their degradation product with end product of intestinal degradation has contributed in their wide acceptance for SNEDDS [29,30]. The semi-synthetically derived oils form good emulsification systems when used with a large number of solubility enhancing surfactants approved for oral administration. Using a mixture of oils can also be used to meet optimum properties of the oily phase. Kassem *et al*. [31]. used a mixture of oleic acid and coconut oil (in a ratio of 7.5:2.5 and 6.7:3.3) for the preparation of

Table 2. Examples of marketed formulations formulated as self-emulsifying systems.

Trade name	Active ingredient	Dosage form	Oil/Lipid used	Surfactant/Co-surfactant used	Company	Indication
Neoral	CsA/I	Soft gelatin capsule	Corn oil Mono-, di-, triglycerides	Polyoxyl 40 hydrogenated castor oil	Novartis	Immune suppressant
Sandimmune	CsA/II	Soft gelatin capsule	Corn oil	NA	Novartis	Immune suppressant
Gengraf®	CsA/III	Hard gelatin capsule	Polyoxyl 35 castor oil	PEG Polysorbate 80	Abbott Laboratories	Immune suppressant
Norvir	Ritonavir	Soft gelatin capsule	Polyoxyl 35 castor oil	Oleic acid	Abbott Laboratories	HIV antiviral
Aptivus	Tipranavir	Soft gelatin capsule	Polyoxyl 35 castor oil	PEG 400	Boehringer Ingelheim	HIV antiviral
Fortovase®	Saquinavir	Soft gelatin capsule	Mono- and diglycerides	DL-α-Tocopherol	Hoffmann-La Roche Inc.	HIV antiviral
Agenerase	Amprenavir	Soft gelatin capsule	D-α Tocopheryl PEG 1000 succinate	PEG 400	GlaxoSmithKline	HIV antiviral
Targretin®	Bexarotene	Soft gelatin capsule	Macrogol	Polysorbate	Ligand	Antineoplastic
Rocaltrol®	Calcitriol	Soft gelatin capsule	MC triglycerides	NA	Roche	Calcium regulator
Accutane	Isotretinoin	Soft gelatin capsule	Soybean oil Hydrogenated soybean oil	Partially hydrogenated soybean oil	Roche	Recalcitrant nodular acne
Vesanoid	Tretinoin	Soft gelatin capsule	Soybean oil Hydrogenated soybean oil	NA	Roche	Acute promyelocytic leukemia

CsA: Cyclosporin; MC: Medium-chain; PEG: Polyethylene glycol.

clotrimazole (CT), a lipophilic imidazole derivative with antimycotic action, loaded SNEDDS. The prepared SNEDDS provided satisfactory properties in terms of droplet size, turbidity values and immediate drug release that could increase the bioavailability profile of CT. Basalious *et al.* [32]. used a mixture of Labrafil®/Capmul® in the ratio of 2:1 w/w for preparing SNEDDS to improve dissolution and oral absorption of lacidipinee, a calcium channel blocker.

Prajapati *et al.* [33]. performed a comparative evaluation of mono-, di- and triglyceride of MC fatty acids in order to select component for optimal lipid-based formulation. They found that with same surfactant monoglyceride formed a clear microemulsion while gel phase was formed in case of di- and triglycerides. When a mixture of monoglyceride with di- or triglyceride was used at a ratio of 1:1, the gel phase eliminated and microemulsions were formed. This clearly indicated that using a mixture of lipids is superior to individual lipid alone.

Thomas *et al.* studied the influence of lipid composition and drug load on the *in vitro* performance of SNEDDS and found that triglyceride chain length can influence the amount of drug that can be loaded in SNEDDS formulation. When Cremophor RH is used as surfactant, MC lipids could dissolve more simvastatin compared with those formulated using LC lipids [19]. In addition, since MC triglycerides are not subject to oxidation, they are popular choice for use in lipid-based products.

4.3 Surfactants

Surfactants are essential components in the formulation of SNEDDS, as these provide the emulsifying properties. The type of surfactant and concentration of the surfactant in the SNEDDS has considerable influence on the droplet size of the formed nanoemulsions. The two important factors that are to be considered while selecting a surfactant are its HLB value and concentration. The HLB of a surfactant gives vital information on its potential utility in formulation of SNEDDS. For attaining high emulsifying performance, the emulsifier involved in formulation of SNEDDS should have high HLB (> 12) and high hydrophilicity which assists in formation of small o/w droplets and rapid spreading of formulation in aqueous media. It would keep drug solubilized for a prolonged period of time at the site of absorption for effective absorption, so precipitation of drug compound within GI lumen is prevented. Certain surfactants might cause irritation to the GI mucosa and skin at higher concentrations. In such cases, a mixture of surfactants can be used [34]. Thus, the selection of surfactant is crucial for the formulation of SNEDDS and the surfactant concentration in SNEDDS should be kept at a minimal level as far as possible.

As a general rule, non-ionic and zwitterionic surfactants tend to be less toxic than ionic surfactants and are therefore more widely used as pharmaceutical excipients [35]. Assuming that the surfactants do not degrade into toxic materials, surfactants having biodegradable/chemically unstable linkers

tend to exhibit less chronic toxicity than those that are chemically stable. For example, as a group, the polyoxyethylene *n*-acyl surfactants exhibit ~ 10 times less chronic toxicity than their *n*-alkyl counterparts, mainly due to their quicker degradation time of days as opposed to weeks. When it comes to comparing acute toxicity, the two groups of surfactants exhibit comparable toxicity [36,37].

It has also been shown that micellar solubilization of lipophilic drugs with high concentrations of surfactants in the formulation significantly affected the amount of free drug and extent of absorption [38,39]. The intestinal absorption of griseofulvin in rats was reported to decrease in the presence of 20 mM taurocholate as a result of micellar solubilization [39]. In a study carried out on a formulation of cyclosporin A (CsA) containing surfactant such as Cremophor EL or RH40 and TPGS at concentrations above 0.02% w/v, demonstrated a decrease in permeability of CsA, which was attributed to micellar solubilization [39].

4.4 Co-solvents

Co-solvents such as ethanol, PG and PEG are required to enable the dissolution of large quantities of hydrophilic surfactant. Inclusion of the co-solvents or solubilizers in SNEDDS may result in expansion of self-nanoemulsification region in the phase diagrams. It should be noted while the incorporation of solubilizers can improve drug loading into SNEDDS, they might compromise droplet size of the nanoemulsion in certain cases, as observed by Anton and Vandamme [40]. The lipid mixture with higher surfactant and co-surfactant:oil ratios leads to the formation of SMEDDS [41,42]. Alcohol and other volatile co-solvents have the disadvantage of evaporating into the shell of soft or hard gelatin capsules, leading to precipitation of drug.

5. Phase behavior

The relationship between the phase behavior of a mixture and its composition can be captured with the aid of a phase diagram. The phase behavior of simple nanoemulsion systems comprising oil, water and surfactant can be studied with the aid of ternary phase diagram in which each corner of the diagram represents 100% of that particular component. More commonly, however, the nanoemulsion will contain additional components such as a co-surfactant and/or drug [37]. When oil, water and surfactants (with or without co-surfactant) are mixed, nanoemulsions are one of a number of association structures (including emulsion, micelles, lamellar, hexagonal and cubic and various gels and oily dispersion) that can form, depending on the chemical composition and concentration of each component [43,44]. In the case where four or more components are investigated, pseudoternary phase diagrams are used where a corner will typically represent a binary mixture of two components such as surfactant/co-surfactant, water/drug or oil/drug. The number of different phases present for a particular mixture can be visually assessed. It should be noted that not every combination of components produce nanoemulsions over the whole range of possible compositions, in some instances the extent of nanoemulsion formation may be very limited.

Construction of phase diagram is a useful approach to illustrate the complex series of interactions that can occur when different components are mixed. Constructing phase diagrams is time consuming, particularly when the aim is to accurately delineate a phase boundary, as the time taken for the system to equilibrate can be greatly increased as the phase boundary is approached. The procedure most often employed is to prepare a series of (pseudo)binary compositions and titrate with the third component, evaluating the mixture after each addition. Care must be taken to ensure not only that the temperature is precisely and accurately controlled, but also that observations are not made on metastable systems [37].

Garti *et al*. [45]. studied the effects of polyols (PG and glycerol) and a short-chain alcohol (ethanol) on the phase behavior of non-ionic and non-ionic/PC (phosphatidylcholine) surfactant mixtures and food grade oils and found that the formulation of food grade o/w microemulsions was difficult to formulate from a three-component systems based on water, oil and single surfactant. However, it was possible to formulate these microemulsions by using a suitable non-ionic surfactant and by the addition of polyols and short-chain alcohols. The phase behavior of the system of *R*(+)-limonene, ethanol, water/PG (1:1) and polyoxyethylene sorbitan monostearate (Tween 60) containing a 1:1:3 *R*(+)-limonene/ethanol/surfactant weight ratio was characterized by a single continuous microemulsion region starting from a pseudobinary solution (surfactant/oil phase) to the microemulsion water/PG (1:1) corner. On dilution, the viscosity measurements indicated that at a certain composition the system inverted from w/o to o/w microemulsion. They proposed that optimal composition of the polar and apolar phases led to formation of a large isotropic area with a high content of solubilized oil.

At low surfactant concentration multiple phases may exist. Within this region and other multiphase regions of the ternary phase diagram, nanoemulsion can exist in equilibrium with the excess water or oil phase, these phases are referred to as Winsor phases [37,43,44,46]:

1. Winsor I: With two phases, the lower (o/w) nanoemulsion phase in equilibrium with the upper excess oil.
2. Winsor II: With two phases, the upper (w/o) nanoemulsion phase in equilibrium with the lower excess water.
3. Winsor III: With three phases, middle nanoemulsion phase (o/w plus w/o, called bicontinuous) in equilibrium with upper excess oil and lower excess water.
4. Winsor IV: In single phase, with oil, water and surfactant homogeneously mixed. In the Winsor classification, the one phase nanoemulsions that are generally explored as drug delivery systems are known as Winsor IV systems.

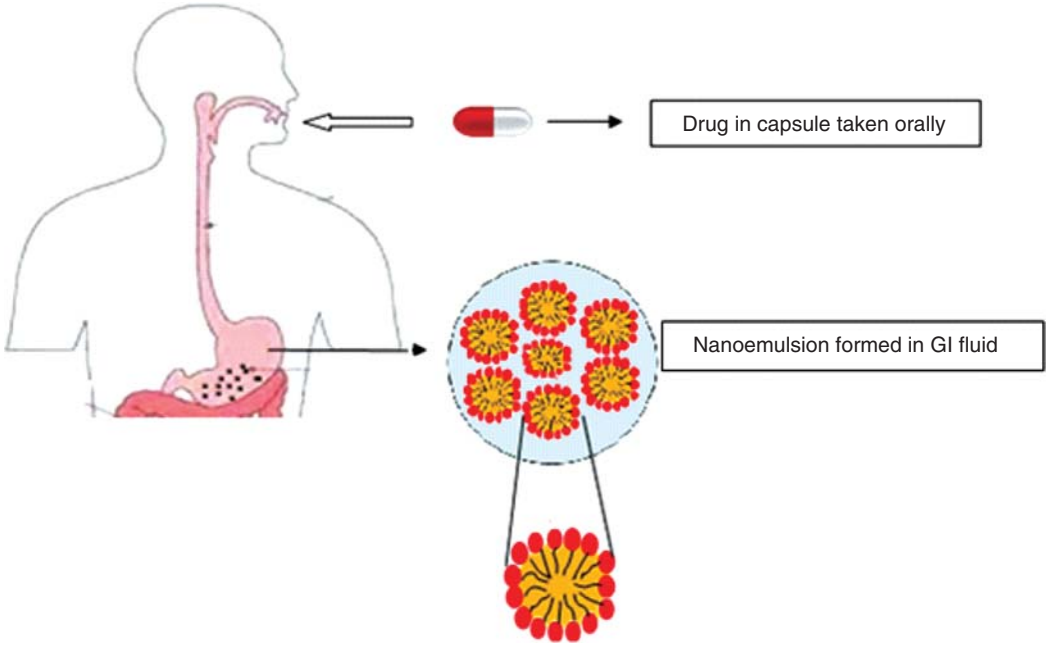

Figure 1. Process of nanoemulsion formation from SNEDDS taken orally.

6. Mechanism of self-emulsification

The mechanism by which self-emulsification take place is not fully understood. Spontaneous emulsification is produced by different mechanisms which seem to be affected by the system composition, the physicochemical characteristics and the protocol of emulsification (i.e., the way in which the components are added and how the thermodynamic properties of the system are changed).

The thermodynamic treatment of conventional emulsion formation has been described by Reiss [47], where the free energy of emulsion formation is a direct function of the energy required to create a new surface between the formed phases. This can be given as:

$$\Delta G = \sum_i (N_i 4\pi r_i^2 \sigma)$$

Where ΔG is the free energy associated with the process, N is the number of droplets of radius r and σ is the interfacial energy. Formed phases will tend to separate over time in order to reduce the interfacial energy, and hence reduce the free energy of the system. Conventional emulsifying agents such as surfactants reduce the interfacial energy by forming a layer around the emulsion particles, which in turn provides a barrier to coalescence. In this case, however, the separation of the phases is merely being delayed as these emulsions are still thermodynamically unstable. In the case of self-emulsifying systems, the free energy required to form the emulsion is either very low or negative when the formation is thermodynamically spontaneous. It was reported by Groves and Galindez [48] and Wakerly *et al.* [49]. that a liquid crystalline phase formed between the oil/surfactant and water phases effectively swells, thereby allowing spontaneous formation of an interface between the oil droplets and water.

The combination of particle size analysis and low frequency dielectric spectroscopy was used by Craig *et al.* [50]. to examine the self-emulsifying properties of a series of IMWITOR 742 (is a blend of mono-, di- and triglycerides of capric and caprylic acids)/Tween 80 systems [50-52]. The dielectric studies gave evidence that the formation of the emulsions may be associated with liquid crystalline phase formation, although the relationship was clearly complex [52]. **Figure 1** describes the process of nanoemulsion formation from SNEDDS taken orally.

Solans and collaborators [53,54] studied the formation of nanoemulsions in a system consisting of water/Brij 30/decane at 25°C by three low-energy emulsification methods. In the first method, oil was added stepwise to a water–surfactant mixture, the second method was stepwise addition of water to a solution of the surfactant in oil and in third method all the components were mixed together. The emulsion composition had a 5.0% by weight surfactant and an oil weight fraction, ranging between 0.2 and 0.8. They obtained nanoemulsions with average droplet size of 50 nm and high kinetic stability only with second method, at oil weight fractions, lower than 0.3. Independent of oil fraction, emulsions obtained by method 2 had lower polydispersity than those obtained by methods 1 and 3.

Similarly, Sole *et al.* [55]. also studied the effect of different dilution procedures on the formation of nanoemulsions obtained by dilution of w/o and o/w microemulsions in the water/SDS (sodium dodecyl sulfate)/co-surfactant/dodecane system, with hexanol or pentanol as co-surfactants. They found that dilution with water induced part of the co-

surfactant molecules to dissolve into water, and the system became thermodynamically unstable giving rise to the nanoemulsion droplets.

7. Characterization of SNEDDS

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

7.1 Determination of emulsification time

In order to quantify the efficiency of emulsification of system comprising Tween 85 with MC triglyceride, Pouton [56] utilized rotating paddle to promote emulsification in crude nephelometer. This enabled an estimation of the time taken for emulsification. On completion of emulsification, samples were taken for particle sizing by photon correlation spectroscopy and self-emulsified systems were compared with homogenized systems. The process of self-emulsification was observed using light microscopy. The mechanism of emulsification was found to involve erosion of a fine cloud of small particles from the surface of large droplets, rather than a progressive reduction in droplet size.

7.2 Droplet size

Droplet size is a decisive factor in self-emulsification performance because it determines the rate and extent of drug release, as well as the stability of the emulsion. The techniques that are mainly used for the determination of droplet size are photon correlation spectroscopy, microscopic techniques or a Coulter Nanosizer [57,58]. Wang *et al*. found that the ibuprofen release rate relied on the mean droplet size of carrier emulsions generated from SNEDDS in dilute media. SNEDDS that yielded nanoemulsion of droplet size 58 nm released more than 95% of the encapsulated ibuprofen within 30 min, which was significantly faster than the control experiment using a conventional tablet [59].

7.3 Turbidity measurement

This identifies efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time [60]. These measurements are carried out on turbidity meters, most commonly the Hach turbidity meter and the Orbeco-Helle turbidity meter [61,62]. In this method to determine clarity of nano- or microemulsion formed and emulsification time, the apparatus is connected to a dissolution apparatus and optical clarity of formulation is taken every 15 s. Turbidity can also be observed in terms of spectroscopic characterization of optical clarity (i.e., absorbance of suitably diluted aqueous dispersion at 400 nm) [63].

7.4 Zeta potential

The charge of the oil droplets is another property that should be assed. In conventional SNEDDS, the charge on an oil droplet is negative because of the presence of free fatty acids [64]. Since SNEDDS are preconcentrate mixture of drug in oil and surfactant and emulsify *in vivo* only, some investigators consider zeta potential as secondary characterization parameter.

7.5 Dispersibility tests

The efficiency of self-emulsification is assessed using the standard European Pharmacopoeia (Ph. Eur., 2008) dissolution apparatus 2 (Erweka, Germany). One milliliter of each formulation was added drop wise to 200 ml of simulated intestinal fluid (SIF) pH 6.8 without enzymes at 37°C. A standard stainless steel dissolution paddle rotating at 60 rpm provides the gentle agitation. Precipitation was evaluated by visual inspection of the resultant emulsion after 24 h. The formulations were then categorized according to their appearance as whitish, dull white and milky, and stable (no precipitation after 24 h) or unstable (showing precipitation within 24 h) [65].

8. Applications of SNEDDS

8.1 Application to drug delivery

To improve the solubility and dissolution of lutein, a naturally occurring oxygenated carotenoid that acts as a potent antioxidant and effective screening agent of high energy blue light and plays important role in the prevention of age-related macular degeneration (AMD), cataracts and other blinding disorders, Yoo *et al*. [66]. prepared SNEDDS that consists of Phosal 53 MCT as oily phase, Labrasol as surfactant and Transcutol-HP as co-surfactant. The prepared formulation consists of 25% oil, 60% surfactant and 15% co-surfactant. Immediate dissolution of drug within 5 min was obtained from the optimized SNEDD formulation which was mixed with Aerosil 200 to solidify it, while there was no dissolution from lutein powder or a commercial product (Eyelac®).

In order to improve the problems associated with the delivery of Gliclazide, an antidiabetic drug, Wankhade *et al*. [67]. developed SNEDDS formulation. Gliclazide showed poorly bioavailability and pH-dependent solubility. The developed formulation consisting of Cremophor EL, Akoline MCM and Caproyl 90 as oily phase, surfactant and co-surfactant yielded nanoemulsion with mean globule size 146 nm, which was not affected by the pH of dilution medium. The optimized SNEDDS released the Gliclazide drug completely within 20 min irrespective of the pH of dissolution medium.

8.2 Improvement in solubility and bioavailability

Incorporation of a drug into a SNEDDS improves the solubility and hence the bioavailability of drug as the dissolution step is bypassed. The drug is presented solubilized in the carries at the site of absorption, which makes it easy to cross the biological membrane and reach the site of action. Ketoprofen, a moderately hydrophobic (logP 0.979)

non-steroidal anti-inflammatory drug (NSAID), is a drug of choice for sustained-release formulation that has high potential for gastric irritation during chronic therapy. Also because of its low solubility, ketoprofen shows incomplete release from sustained release formulations. Different formulation approaches that have been sought to achieve sustained release, increase the bioavailability, and decrease in the gastric irritation of ketoprofen include preparation of matrix pellets of nanocrystalline ketoprofen, sustained-release ketoprofen microparticles and formulations, floating oral ketoprofen systems and transdermal systems of ketoprofen.

Preparation and stabilization of nanocrystalline or improved solubility forms of drug may pose processing, stability and economic problems. This problem can be successfully overcome when ketoprofen is presented in self-emulsifying formulation. This formulation enhanced bioavailability due to increase in the solubility of drug and minimizes the gastric irritation. Also incorporation of gelling agent in SEDDS sustained the release of ketoprofen [68].

In SNEDDS, the lipid matrix interacts readily with water, forming a fine particulate o/w emulsion. The emulsion droplets will deliver the drug to the GI mucosa in the dissolved state readily accessible for absorption. Therefore, increase in area under curve (AUC), that is, bioavailability and C_{max} is observed with many drugs when presented in SNEDDS.

Lipid-based formulations have showed a great potential to improve the bioavailability of chemotherapeutic drug. Hanan and El-Laithy [69] developed SNEDDS containing biphenyl dimethyl dicarboxylate (BDD), a hepatoprotector that is currently employed as an agent against virally induced hepatic injury, using Tween 80 to Transcutol as surfactant and cosurfactant, respectively and Miglyol 812 as oil and found that the oral absorption and bioavailability of SNEDDS containing BDD in albino rats were significantly enhanced ($p < 0.01$) with an average improvement of 1.7- and 6-fold that of commercial Chinese pilules® and Pennel capsules®, respectively. The study revealed the potentials of self-emulsifying system over the orally administered conventional formulations.

Similarly, Zhao *et al*. observed an increase of 1.7- and 2.5-fold in AUC and C_{max}, respectively when Zedoary turmeric oil (ZTO), an essential oil extracted from the dry rhizome of *Curcuma zedoaria* was administered as SNEDDS orally to rats [70]. The optimized formulation consisted of ZTO, ethyl oleate, Tween 80, Transcutol P in a ratio of 30.8:7.7:40.5:21 w/w, respectively.

Khoo *et al*. [71]. reported the preparation of a halofantrine-containing lipid-based solid self-emulsifying system using either vitamin E TPGS or a blend of Gelucire 44:14 and Vitamin E TPGS as the base. On dispersal, these systems produced dispersions that the authors described as microemulsions. Studies in fasted dogs showed that these solid dispersions exhibited a five- to sevenfold improvement in absolute oral bioavailability, when compared with the commercially available tablet formulation.

In a different approach, Nazzal *et al*. [72]. determined the potential of a reversibly induced re-crystallized semi-solid SNEDDS, based on a eutectic interaction between the drug and the carrying agent, as an alternative to a conventional SEDDS. In these eutectic-based self-nanoemulsified systems, the melting point depression method allows the oil phase containing the drug itself to melt at body temperature from its semi-solid consistency, and disperse to form emulsion droplets in the nanometer size range. Emulsion systems based on a eutectic mixture of lidocaine–prilocaine [73] and lidocaine–menthol [74] have been used in the preparation of topical formulations. However, little is known of the use of eutectic mixtures for the preparation of self-(micro)emulsified formulations.

8.3 Protection against biodegradation

The ability of self-emulsifying drug delivery system to reduce degradation as well as improve absorption may be especially useful for drugs, for which both low solubility and degradation in the GI tract contribute to a low oral bioavailability. Many drugs are degraded in physiological system, may be because of acidic pH in stomach, enzymatic degradation or hydrolytic degradation, etc. Such drugs when presented in the form of SNEDDS can be well protected against these degradation processes as liquid crystalline phase in SNEDDS might act as barrier between degrading environment and the drug. Acetylsalicylic acid (logP = 1.2, Mw = 180), is readily hydrolyzed to salicylic acid in the acidic environment of GI tract and show degradation in the GI tract. When the drug was formulated in a Galacticles™ Oral Lipid Matrix System (SEDDS formulation) and compared with a commercial formulation, it showed the good plasma profile as compared with reference formulation. The oral bioavailability of undegraded acetylsalicylic acid improved by 73% by the Galacticles™ Oral Lipid Matrix System formulation compared with the reference formulation. This suggests that the self-emulsifying formulation has a capacity to protect drugs from degradation in the GI tract. Supersaturable SEDDS contain a reduced amount of a surfactant and a water-soluble cellulosic polymer (or other polymers) to prevent precipitation of the drug by generating and maintaining a supersaturated state *in vivo*.

An approach which will increase drug solubility and protect drug from degradation by cholinesterase in intestinal washings is highly desirable for optimizing the therapeutic performance of cefpodoxime proxetil (CFP), a poorly bioavailable high-dose antibiotic having pH-dependent solubility. Date and Nagarsenker [75] developed CFP SNEDDS consisting of Cremophor EL, Akoline MCM and Capryol 90 that yielded nanoemulsion of mean globule size 170 nm, released CFP completely within 20 min. The system provided 100% release which is independent of pH of dissolution media.

9. Biological aspects in selection of SNEDDS

Very few biopharmaceutical studies have been performed with SNEDDS [76], and there is a need for more comparative

studies, particularly against simple oils and solid dosage forms. At this stage, however, it is worth speculating on the issues that will influence the absorption from SNEDDS [77]. The rate of gastric emptying of SNEDDS is similar to solutions, so they are particularly useful where rapid onset of action is desirable. Conversely, if the therapeutic index of the drug is low, the rapid onset and accompanying high T_{half} might lead to undesirable side effects. With regard to bioavailability, there are differences between formulations that contain water-soluble surfactants or co-solvents and those that do not. The former systems can produce emulsions or micellar solutions with a lower capacity for solubilization of drugs, which might result in precipitation of drugs in the gut. SNEDDS formed with relatively hydrophobic surfactants (HLB 8 – 12), such as Tween 85 or Tagat TO, which do not migrate into the aqueous phase, tend to have lower solvent capacities for drugs unless logP (drug) > 4. These SNEDDS should be preferable, however, if the drug can be dissolved to an adequate extent. Highly potent but poorly water-soluble drug candidates are a common outcome of contemporary drug discovery programs and present several challenges to drug development, most notably, the issue of reduced systemic exposure after oral administration [78].

10. Future trends

In relation to formulation development of poorly soluble drugs in the future, there are now techniques being used to convert liquid/semi-solid SNEDDS formulations into powders and granules, which can then be further processed into conventional 'powder-fill' capsules or even compressed into tablets. There is also increasing interest in using inert adsorbents, such as the Neusilin (Fuji Chemicals, Toyama, Japan) and Zeopharm (J.M. Huber Corp., Edison, NJ, USA) products for converting liquids into powders that help in formulation of solid SNEDDS. But to obtain solid SNEDDS with suitable processing properties, the ratio of SNEDDS to solidifying excipients must be very high [79], which seems to be practically non-feasible for drugs having limited solubility in oil phase. In this regard, it was hypothesized that the amount of solidifying excipients required for transformation of SNEDDS in solid dosage forms will be significantly reduced if SNEDDS is gelled. Colloidal silicon dioxide (Aerosil 200) is selected as a gelling agent for the oil-based systems, which may serve the dual purpose of reducing the amount of solidifying excipients required and aiding in slowing drug release.

11. Expert opinion

Recently, lipid-based drug delivery systems have been getting more attention among scientists for the development of formulations, for poorly water-soluble drugs. Successful large-scale production of the SNEDDS exemplified by immunosuppressive agent CsA (Neoral, 165 Novartis Pharmaceuticals Corp., East Hanover, NJ, USA), and for the two HIV protease inhibitors ritonavir (Norvir, Abbott Laboratories, Abbott Park, IL, USA) and saquinavir (Fortovase, Roche Pharmaceuticals, Nutley, NJ, USA), has generated considerable interest not only among the scientists community but also among different pharmaceutical companies. These systems offer a number of advantages including maintenance of dose and stability among several others. The high drug-loading efficiency and positive food effect make them unique system for the enhancing absorption of poorly soluble drugs (BCS class II and class IV). However, a considerable gap exists between the need for lipid-based drug delivery systems and their application, as reflected by the low number of marketed drug products relying on oral lipid-based formulations. Questions regarding the physical and chemical stability of drugs solubilized in lipid and excipients mixture have not yet been adequately addressed. These formulations must be designed to work in harmony with the physiological environment.

Formulating a lipophilic drug as SNEDDS requires careful selection of the components. From the formulation point of view, it is necessary to consider the emulsification properties of lipid vehicle and the solubility of drug in an oil or oil–surfactant mixture. Since the concentration of surfactants is high in SNEDDS, chronic use of these systems requires careful monitoring. The regulatory status of various ingredients and their safety are of prime concern. The physical and chemical changes in the excipients over time could potentially impact drug stability and formulation performance with time. The incorporation of bioactive excipients should be explored, and known biochemical processes in the GI tract should be exploited. Self-emulsifying drug delivery system in solid dosage form has improved solubility/dissolution, absorption and bioavailability for poorly water-soluble drug. The area of solid SNEDDS is to be explored for development into different solid dosage form for oral and parenteral administrations.

In future, effective tests should be developed and utilized to understand and predict the *in vivo* behavior of these systems. The role of individual component in dispersion process, drug solubilization and emulsion formation should be the focus area.

Declaration of interest

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