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A REVIEW ON FORMULATION TECHNIQUES OF SOLID SELF NANOEMULSIFYING DRUG DELIVERY SYSTYM

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Abstract: Self-nanoemulsifying drug delivery systems are a vital tool in solving low bioavailability issues of poorly soluble drugs. Hydrophobic drugs can be dissolved in these systems, enabling them to be administered as a unit dosage form for per-oral administration. The efficiency of oral absorption of the drug compound from the Self-nanoemulsifying drug delivery systems (SNEDDS) depends on many formulation−related parameters, such as surfactant concentration, oil/surfactant ratio, polarity of the emulsion, droplet size and charge, all of which in essence determine the self-nanoemulsification ability. Thus, only very specific pharmaceutical excipient combinations will lead to efficient self-nanoemulsifying systems. SNEDDS can improve oral bioavailability of hydrophobic drugs by several mechanisms. The conversion of liquid SNEDDS to solid oral dosage forms or solid SNEDDS has also been achieved by researchers. Solid SNEDDS can offer better patient compliance and minimize problems associated with capsules filled with liquid SNEDDS. The fact that almost 40% of the new drug compounds are hydrophobic in nature implies that studies with Solid Self-nanoemulsifying drug delivery systems (S-SNEDDS) will continue, and more drug compounds formulated as S-SNEDDS will reach the pharmaceutical market in the future.

Keywords: Self-nanoemulsification, hydrophobicity, liquid SNEDDS, solidification techniques, S-SNEDDS, oral bioavailability

1 INTRODUCTION:

Nearly 50% of the new drug candidates that reach formulation scientists have poor water solubility, and oral delivery of such drugs is frequently associated with low bioavailability [1, 2]. To overcome these problems, various formulation strategies have been exploited, such as the use of surfactants, lipids, permeation enhancers, micronization, salt formulation, cyclodextrins, and nanoparticles solid dispersions. The availability of the drug for absorption can be enhanced by presentation of the drug as a solubilizate within a colloidal dispersion. Much attention has focused on lipid solutions, emulsions and emulsion preconcentrates, which can be prepared as physically stable formulations suitable for encapsulation of such poorly soluble drugs. Emulsion systems are associated with their own set of complexities, including stability and manufacturing problems associated with their commercial production. Self-emulsification systems are one formulation technique that can be a fitting answer to such problems [3, 4]. These systems includes Self microemulsifying drug delivery system (SMEDDS) and self nanoemulsifying drug delivery system (SNEDDS).

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Nanotechnology has become a buzzword in pharmaceutical sciences and efforts are ongoing to extend its applications in various streams of pharmaceutical sciences. Nanotechnology has dramatically influenced drug delivery research over the last two decades and several nanoscale technologies/carriers have been and are being explored for improving therapeutic performance of drugs [5].SNEDDS are nanoemulsion preconcentrates or anhydrous forms of nanoemulsion. These systems are anhydrous isotropic mixtures of oil, surfactant(s) and drug, which, when introduced into aqueous phase under conditions of gentle agitation, spontaneously form O/W nanoemulsions (usually with globule size less than 200 nm) [6]. In the body, the agitation required for formation of nanoemulsions is provided by digestive motility of the GI tract. SNEDDS can also contain coemulsifier or cosurfactant and/or solubilizer in order to facilitate nanoemulsification or improve the drug incorporation in SNEDDS.

Compared with ready to use nanoemulsions, SNEDDS can offer advantages such as [7]:

- Improved physical and/or chemical stability profile upon long term Storage
- Possibility of filling them into unit dosage forms, such as soft/hard gelatin or hydroxypropyl methylcellulose capsules (unlike ready to use

nanoemulsions), which improves their commercial viability and patient compliance/acceptability;

- No palatability related issues, as SNEDDS can be filled into capsules.

Formulation Considerations [7]:

Successful formulation of SNEDDS depends on the thorough understanding of the spontaneous nanoemulsification process and also on the physicochemical and biological properties of the components used for the fabrication of SNEDDS. The factors influencing the phenomenon of self nanoemulsification are:

- The physicochemical nature and concentration of oily phase, surfactant and coemulsifier or cosurfactant or solubilizer (if included)
- The ratio of the components, especially oil to surfactant ratio
- The temperature and pH of the aqueous phase where nanoemulsification would occur
- Physicochemical properties of the drug, such as hydrophilicity/lipophilicity, pKa and polarity.

These factors should receive attention while formulating SNEDDS. In addition, the acceptability of the SNEDDS components for the desired route of administration is also very important while formulating SNEDDS.

2 POTENTIAL COMPONENTS:

a) **Drug :** It is important to know that the therapeutic agent of interest can also have significant impact on the various aspects of SNEDDS, such as phase behaviour and nanoemulsion droplet size. Various physicochemical properties of the drug, such as log P, pKa, molecular structure and weight, presence of ionisable groups and also the quantity have considerable effects on the performance of SNEDDS.[7] Lipid based compound forms a possible platform for improving oral bioavailability of drug belonging to BCS class II and IV. For formulation of SMEDDS Log P value should be 2-4. Dose of API and melting point should be high [36].

Table 1: Application of SEDDS in various BCS category drugs [40]

BCS class	Problems
Class I	Enzymatic degradation, gut wall efflux
Class II	Solubilization and bioavailability
Class III	Enzymatic degradation, gut wall efflux and bioavailability
Class IV	Solubilization, enzymatic degradation, gut wall efflux and bioavailability

b) Oil phase

The oil represents one of the most important excipients in the SNEDDS formulation not only because it can solubilize marked amounts of the lipophilic drug or facilitate self emulsification but also and mainly because it can increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract depending on the molecular nature of the triglyceride [13, 14, 15, 16]. oil phase has great importance in the formulation of SNEDDS as physicochemical properties of oil (e.g., molecular volume, polarity and viscosity) significantly govern the spontaneity of the nanoemulsification process, droplet size of the nanoemulsion, drug solubility and biological fate of nanoemulsions and drug[8,9,10,11,12]. Usually, the oil, which has maximum Solubilizing potential for the selected drug candidate, is selected as an oily phase for the formulation of SNEDDS. This helps to achieve the maximal drug loading in the SNEDDS. At the same time, the selected oil should be able to yield nanoemulsions with small droplet size. Hence, the choice of the oily phase is often a compromise between its ability to solubilize the drug and its ability to facilitate formation of nanoemulsion with desired characteristics. It is a known fact that oils with excessively long hydrocarbon chains, such as fixed oils (e.g., soybean oil) or long chain triglycerides, are difficult to nanoemulsify, whereas oils with moderate chain length (medium chain triglycerides) and oils with short chains (or low molecular volume), such as medium chain monoglycerides and fatty acid esters (e.g., ethyl oleate), are easy to nanoemulsify compared with long chain triglycerides. The lipophilicity of the oil and concentration of oily phase in SNEDDS are directly proportional to the nanoemulsion size [10]. Interestingly, long chain triglycerides have demonstrated great ability to improve intestinal lymphatic transport of drugs (responsible for preventing first pass metabolism of drugs) compared with medium chain tri, di and monoglycerides, whereas medium chain mono and di glycerides have greater solubilization potential for hydrophobic drugs and permeation enhancing properties[17,18,19]. Furthermore, edible oils which could represent the logical and preferred lipid excipient choice for the development of SEDDS are not frequently selected due to their poor ability to dissolve large amounts of lipophilic drugs. Modified or hydrolyzed vegetable oils have been widely used since these excipients form good

emulsification systems with a large number of surfactants approved for oral administration and exhibit better drug solubility properties [11].

Table2. Commonly used oily phases [7]

General class	Commercial class	Examples	Acceptability
Fixed oils	Soybean oil, castor oil	-	P/O/T/Oc/M
MCTs	Triglycerides of apric/caprylic acids	Miglyol 810, 812, Labrafac CC Crodamol GTCC, Captex 300, 355	P/O/T/Oc/M
	Triacetin	Captex 500	
Medium chain Mono and Di glycerides	Mono and Di glycerides Of capric/ caprylic acids	Capmul MCM, Imwitor 742, Akoline MCM	O/T
Long chain Mono glycerides	Glyceryl monooleate	Peceol, Capmul GMO	O/T
Glyceryl mono linoleate	Maisine35	-	O/T
PG fatty acid esters	PG monocaprylate	Capryol 90, capmul pg 8, sefsol 21	O/T
	PG mono laurate/ dilaurat	Lauroglycol 90, Capmul PG12, Lauroglycol FCC	
	PG dicaprylate/caprate	Miglyol 840, Captex 200	
Fatty acid esters	Ethyl oleate	Crodamol EO	P//T/Oc/M
	Isopropyl myristate	-	
	Isopropyl palmitate	-	
Fatty acids	Oleic acid	Crossential O94	O/T/M
	Caprylic acid	-	
Vitamins	Vitamin E	-	P/O/T/Oc/M

M : Mucosal; MCT: Medium chain triglyceride; O: Oral; Oc: Ocular; P: Parenteral; PG: Propylene glycol; T: Topical (dermal)

c) Surfactant

Several compounds exhibiting surfactant properties may be employed for the design of self-emulsifying systems, the most widely recommended ones being the non-ionic surfactants with a relatively high hydrophilic−lipophilic balance (HLB) [11]. The properties of the surfactant, such as HLB (in oil), cloud point, viscosity and affinity for the oily phase, have great influence on the nanoemulsification process, self nanoemulsification region and the droplet size of nanoemulsion.[6,21-23] The concentration of the surfactant in the SNEDDS has considerable influence on the droplet size of nanoemulsion.[20,21] The acceptability of the selected surfactant for the desired route of administration and its regulatory status (e.g., generally regarded as safe [GRAS] status) must also be considered during surfactant selection. Many nonionic surfactants, such as Ctenophore EL (polyethylene glycol [PEG], castor oil), have the ability to enhance permeability and uptake of drugs that are susceptible to P-glycoprotein mediated efflux. [24-26]. The surfactant involved in the formulation of SNEDDS should have a relatively high HLB and

hydrophilicity so that immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media (good self-emulsifying performance) can be achieved. For an effective absorption, the precipitation of the drug compound within the GI lumen should be prevented and the drug should be kept solubilized for a prolonged period of time at the site of absorption [11].

- To modulate self nanoemulsification time of the SNEDDS;
- To modulate droplet size of nanoemulsion.

Table 3: Commonly used surfactants [7]

General class	Examples	Commercial name	Acceptability
Polysorbates	POE20sorbitan monooleate	Tween® 80, Crillet 4	P/O/T/Oc/M
	POE20sorbitan monolaurate	Tween 20, Crillet 1	
Sorbitan esters	Sorbitan monooleate	Span® 80, Crill 4	P/O/T/Oc/M
	Sorbitan monolaurate	Span 20, Crill 1	
	Sorbitan monostearate	Span 60, Crill 3	O/T/M
PEO–PPO–block copolymers	Poloxamer 188	Pluronic®/LutrolF 68	P/O/T/Oc/M
	Poloxamer 407	Pluronic/Lutrol F 127	O/T/Oc/M
POE castor oil	POE35castor oil	Cremphor® EL, Etocas 35 HV	P/O/T/Oc/M
POE hydrogenated castor oil	POE40hydrogenated castor oil	Cremophor RH 40, HCO40,Croduret40	LD P/O/T/Oc/M
	POE60hydrogenated castor oil	Cremophor RH 60, HCO60	P/O/T/Oc/M
POE stearate	PEG66012hydroxy stearate	Solutol HS 15®	P/O/T/Oc/M
POE vitamin E	Tocopheryl PEG 1000succinate	Vitamin E TPGS	T/O/Oc/M
Sucrose esters	Sucrose laurate	-	O/T
	Sucrose palmitate	-	O/T
Polyglycolyzed glycerides	Linoleoyl macrogol glycerides	Labrafil® 2125 CS	O/T
	Oleoyl macrogol glycerides	Labrafil 1944 CS	
	Caprylocaproyl macrogol glyceride	Labrasol®	
	Polyglyceryl oleate	Plurol® oleique CC 497	
	Lauroyl macrogol glycerides	Gelucire® 44/14	
Phospholipids	Soybean lecithin	-	All routes

M: Mucosal; O: Oral; Oc: Ocular; P: Parenteral; PEG: Polyethylene glycol; POE: Polyoxyethylene; T: Topical (dermal) ; TPGS: Tocopheryl polyethylene glycol 1000 succinate.

d) Co-surfactant co-emulsifyer or solubilizers

The production of an optimum SNEDDS requires relatively high concentrations (generally more than 30% w/w) of surfactants. [11] Co emulsifiers, co surfactants or solubilizers are typically employed in the SNEDDS for pharmaceutical use as follows;

- To increase the drug loading to SNEDDS;

Table 4: List of commonly used solubilizers [7]

General class	Examples	Acceptability
Short chain alcohols	Ethanol, benzyl alcohol	P/O/T/Oc/M
Alkane diols and triols	Propylene glycol Glycerol	P/O/T/Oc/M
Polyethylene glycols	PEG 400	P/O/T/Oc/M
Glycol ethers	Diethylene glycol monoethyl ether (Transcutol®)	O/T

DRUG LOADING:

Drugs with low aqueous solubility present a major challenge during formulation as their high hydrophobicity prevents them from being dissolved in most approved solvents. The novel synthetic hydrophilic oils and surfactants usually dissolve hydrophobic drugs to a greater extent than conventional vegetable oils. The efficiency of drug incorporation into a SEDDS is generally specific to each case depending on the physicochemical compatibility of the drug/system. In most cases, there is an interference of the drug with the self-emulsification process up to a certain extent leading to a change in the optimal oil/surfactant ratio. The efficiency of a SEDDS can be altered either by halting charge movement through the system by direct complexation of the drug compound with some of the components in the mixture through its interaction with the LC phase [42],or by penetration into the surfactant interfacial monolayer [41].The interference of the drug compound with the self-emulsification process may result in a change in droplet size distribution that can vary as a function of drug concentration [41].It should be pointed out that emulsions with smaller oil droplets in more complex formulations are more prone to changes caused by addition of the drug compound. Hence, the design of an optimal SEDDS requires pre-formulation solubility and phase diagram studies to be conducted.

MECHANISM OF SELF-EMULSIFICATION:

According to Reiss [38], self-emulsification occurs when the entropy change that favours dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of the conventional emulsion is a direct function of the energy required to create a new surface between the oil and water phases and can be described by the equation:

DG = SNi pri2S

Where DG is the free energy associated with the process (ignoring the free energy of mixing), N is the number of droplets of radius r and S represents the interfacial energy. The two phases of emulsion tend to separate with time to reduce the interfacial area and, subsequently, the emulsion is stabilized by emulsifying agents, who form a monolayer of emulsion droplets, and hence reduces the interfacial energy, as well as providing a barrier to prevent coalescence [39].

Table5. Commercial nanoemulsion formulations [43]:

Drug/Bioactive	Brand Name	Manufacturer	Indication
Palmitate alprostadil	Liple	Mitsubishi Pharmaceutical , Japan	Vasodilator , platelet inhibitor
Dexamethason	Limethason	Mitsubishi Pharmaceutical , Japan	Steroid
Propofol	Diprivan	Astra Zaneca	Anaesthetic
Flurbiprofenaxtil	Ropion	Kaken Pharmaceutical , Japan	NSAID
Vitamins A, D, E and K	Vitalipid	Fresenius Kabi Europe	Parenteral nutrition

LIMITATIONS OF LIQUID SNEDDS [7]:

Self nanoemulsifying drug delivery systems, being liquid in nature, need to be delivered through either soft/hard gelatin or hydroxypropyl methylcellulose capsules. There are few issues associated with these systems when presented in capsules, such as

- Incompatibility of components with the capsule shell in the long term
- precipitation of drugs during fabrication storage at low
- temperature and critical method of production
- SNEDDS may not be useful for hydrophobic drugs that can undergo pH catalyzed or solution state degradation

SOLIDIFICATION TECHNIQUES OF LIQUID SNEDDS:

Solid SNEDDS was developed in order to eliminate the disadvantages associated with liquid SNEDDS handling, manufacturing and stability. Solid SNEDDS in the form of dry, solid powders would help in overcoming the limitations associated with liquid SNEDDS. Solid Dosage forms are most stable and are convenient for handling; therefore, attempts are made to convert the liquid systems into solid SNEDDS. [27]

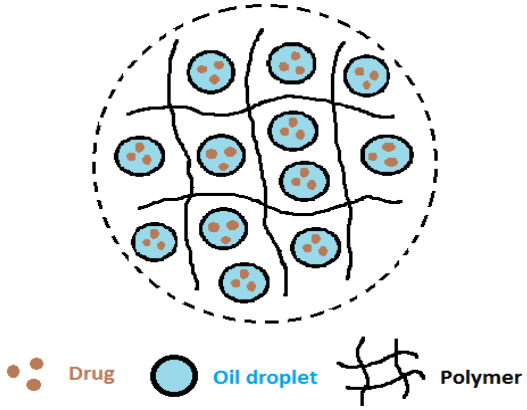

Fig.1. Solidification of liquid SNEDDS

• **Capsule filling with liquid and semisolid self-emulsifying formulations:** Capsule filling is the simplest and the most common technology for the encapsulation of liquid or semi solid SE formulations for the oral route. The advantages of capsule filling are simplicity of manufacturing, suitability for low-dose highly potent

drugs and high drug loading up to 50% (w/w) potential [28].

• **Spray drying:** This technique involves the preparation of a formulation by mixing lipids, surfactants, drug, solid carriers, and solubilization of the mixture before spray drying. The solubilized liquid formulation is then atomized into a spray of droplets. The droplets are introduced into a drying chamber, where the volatile phase (e.g. the water contained in an emulsion) evaporates, forming dry particles under controlled temperature and airflow conditions. Such particles can be further prepared into tablets or capsules [28].

• **Spray cooling:** Spray cooling also referred to as spray congealing is a process whereby the molten formula is sprayed into a cooling chamber. Upon contact with the cooling air, the molten droplets congeal and re-crystallize into spherical solid particles that fall to the bottom of the chamber and subsequently collected as fine powder. The fine powder may then be used for development of solid dosage forms, tablets or direct filling into hard shell capsules. Many types of equipment are available to atomize the liquid mixture and to generate droplets: rotary pressure, two-fluid or ultrasonic atomizers [29, 30].

• **Adsorption to solid carriers:** SEDDS can be adsorbed at high levels (up to 70% (w/w)) onto suitable carriers. Solid carriers can be microporous inorganic substances, high surface area colloidal inorganic adsorbent substances, cross-linked polymers or nanoparticle adsorbents (e.g., silica, silicates, magnesium trisilicate, magnesium hydroxide, talcum, crospovidone, cross-linked sodium carboxymethyl cellulose and cross linked polymethyl methacrylate). The adsorption technique has been successfully applied to gentamicin and erythropoietin with caprylocaproyl polyoxyl glycerides (Labrasol) formulations that maintained their bioavailability enhancing effect after adsorption on carriers [31-33].

• **Melt granulation:** Melt granulation or pelletization is a one step-process allowing the transformation of a powder mix (containing the drug) into granules or spheronized pellets. The technique needs high shear mixing in presence of a meltable binder. This is referred to as "pump on" technique. Alternatively, the binder may be blended with the powder mix in its solid or semi-solid state and allowed to melt (partially or completely) by the heat generated from the friction of particles during high shear mixing referred to as "melt-in" process. The melted binder forms liquid bridges with the powder particles that shape into small agglomerates (granules) which can, by further mixing under controlled conditions transform to spheronized pellets [28].

• **Melt extrusion/Extrusion spheronization:** It is a solvent-free process that allows high drug loading (60%) as well as content uniformity. Applying extrusion-spheronization, SE pellets of diazepam and progesterone and bi-layered cohesive SE pellets have been prepared [34, 35].

Dosage form development of S-SMEDDS [40]:

- Dry emulsions
- Self- nano emulsifying capsules
- Self- nano emulsifying sustained/controlled-release tablets
- Self- nano emulsifying sustained/controlled-release pellets
- Self- nano emulsifying solid dispersions
- Self- nano emulsifying suppositories
- Self- nano emulsifying implants

FUTURE PERSPECTIVES:

S-SNEEDS are proposed for numerous applications in pharmacy as drug delivery systems because of their capacity to hold non-polar active compounds. Future perspectives of S-SNEDDS are very promising in different fields of therapeutics or application in development of solid orals. One of the versatile applications of nanoemulsion is in the area of drug delivery where they act as efficient carriers for bioactives, facilitating administration by oral route. The advantages and applications of S-SNEDDS for oral drug delivery are numerous, where the droplet size is related to their absorption in the gastrointestinal tract. The prospects of S-SNEDDS lie in the ingenuity of formulation experts to utilize the advantages of nano-solid carriers in overcoming peculiar problems of drug delivery such as absorption, permeation and stability of class 3 and 4 hydrophobic drugs.

CONCUSION:

S-SNEDDS are a promising approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SS-SNEDDS, which have been shown to improve oral bioavailability substantially. The efficiency of the S-SNEDDS formulation is case−specific in most instances; thus, composition of the S-SNEDDS formulation should be determined very carefully. Since a relatively high concentration of surfactants is generally employed in the S-NSEDDS formulation, toxicity of the surfactant being used should be taken into account. In fact, a compromise must be reached between the toxicity and self nanoemulsification ability of the surfactant that is considered for use. The size and charge of the oil droplet in the emulsion formed are two other important factors that affect GI absorption efficiency. The nano size of these

formulations is responsible for facilitating enhancement of drug dissolution and absorption, owing to the large surface area. The lipidic nature of these systems allows delivery of drugs to the lymphatic system. However, certain issues, such as drug–excipient interaction, oxidation of vegetable oils, toxicity and safety warrant attention during the development of SNEDDS. The amenability of converting SNEDDS into solid self nanoemulsifying systems enables development into solid dosage form. Thus, the solid self nanoemulsifying system can serve as platform technology for delivering poorly soluble drugs. Although a lot of research is being carried out in this area, other aspects, such as *in vitro/in vivo* correlation, need to be established.

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