"INNOVATIVE DRUG DELIVERY STRATEGIES: UNVEILING THE POTENTIAL OF SELF-EMULSIFICATION"

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Abstract

Challenges encountered in the efficient delivery of drugs are multi-dimensional ranging from solubility issues to the first-pass biotransformation to P-gp efflux-based removal of drugs. Most drugs suffer from one or more of these problems. There are varieties of ways to overcome them. This article provides a comprehensive review of one such approach called "selfies". Selfies are self-emulsifying systems that have the ability to convert into an emulsion with extremely fine droplets of micron or nano sizes. Thereby they give all the benefits of emulsions without the inherent stability issues associated with the dosage form. This review is designed to help formulators see the multifaceted personality of these systems. It is going to highlight the differences between the different selfies, elaborate on the various excipients that are available to make a system as you envision functioning, reflecting on the various applications for which these versatile systems have been used thus far, the assortment of dosage forms into which they have been converted for ease of delivery and lastly, it would focus on the opportunities that lay ahead if one opts for these systems. This would also provide unique areas of research which are hitherto still questions largely unanswered.

Keywords: Bioavailability, Nano formulations, Self-emulsifying system; Self-micro emulsifying; Self-nanoemulsifying; Solubility

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INTRODUCTION

Convenience and patient compliance make oral delivery of drugs by far the most popular mode. But a lot of molecules have not experienced success via the oral route making them difficult to formulate. A lot of new chemical entities fail during the research and development phase as they are deemed unfit for oral drug delivery. Drugs today are plagued with a plethora of problems like but not limited to poor aqueous solubility and poor dissolution rate(1), substantial first-pass metabolism, limited membrane permeability due to improper partition coefficient, efflux of xenobiotics due to P-glycoprotein (P-gp) in the liver, kidney, and intestine and enzymatic as well as pH-dependent degradation of drugs in the gastrointestinal tract (GIT)(2). More than 40% of currently available drugs and over 70% of drugs in the pipeline are touted to be poorly water-soluble which makes them unattractive candidates for oral drug delivery(3). P-gp is a class of ATP-binding cassettes that function primarily as a biological barrier by extruding drugs out of the cells. This is one of the main reasons for the development of drug resistance of anti-cancer drugs(4). Presystemic metabolism is one of the main reasons for the sub-therapeutic action of a drug due to greatly reduced bioavailability which leads to either changing the route of drug administration or adding excess drug as the only two alternatives, both of which are not very attractive. The Biopharmaceutical Classification System (BCS) introduced by Amidon and his team in 1995(5) paved the way to classify the orally administered drugs on basis of their solubility and membrane permeation. It gave 4 broad categories with different combinations of high or low solubility and high or low permeability. It took into consideration that the drug would have to undergo three steps, namely liberation and dissolution in GI fluid, stay dissolved through the entire length of GIT and eventually permeates through biological barriers and become bioavailable. A fourth well-known step of enterohepatic biotransformation wasn't taken into consideration which could not only reduce bioavailability but introduce metabolites into systemic circulation. This was taken into consideration by Wu and Benet (6) while coming up with their Biopharmaceutical Drug Disposition Classification System (BDDCS). BCS does provide an initial framework it also doesn't give complete consideration to solubility behaviour of drugs and hence it is not a complete tool for formulators. This was taken into consideration by Butler and Dressman who proposed a Developability Classification System (DCS) with intended application as a formulation tool which has since been revised by them(7,8).

Over the last couple of decades, lipids have been found to provide acceptable improvement in the delivery of drugs exhibiting poor solubility(9). A surge in development and availability of multi-functional and flexible lipid excipients showing an acceptable safety profile and regulatory approvals have paved a way forward for these systems. They could not only help with solubility enhancement but would also help in bypassing first-pass excretion and efflux due to P-glycoproteins(10). These lipid-based systems could improve the bioavailability of a drug by one or more of the following mechanisms: bypassing dissolution by delivering the drug in a solubilized form and prevention of precipitation of the said molecule, enhancing drug solubilization in GIT as the formulation components digest thereby indirectly recruiting endogenous solubilizers like bile salts and phospholipids, increasing membrane permeability as well as reducing the effect of P-gp and other efflux transporters and lastly manipulating lymphatic uptake of drug thereby avoiding presystemic metabolism of the molecule.

Lipid-based drug delivery systems (LBDDS) is a broad term encompassing oily solutions, coarse emulsions, dispersions, micelles, self-emulsifying drug delivery systems (SEDDS), self-micro emulsifying drug delivery systems (SMEDDS), and self-nanoemulsifying drug delivery system (SNEDDS). LBDDS are a diversified group of formulations that contain some combination of five main ingredients; pure triglyceride oils, mixed glycerides, surfactants of both kinds, and water-soluble co-solvents. Colin Pouton has laid down and further modified a classification system aptly called the Lipid Formulation Classification System (LFCS)(9,11). The key suggestions and pointers from LFCS have been summarised in Table 1 below:

LFCS provides a simple scaffolding that can be used by formulators to predict how the drug's disposition in vivo be affected by formulation and to optimize the selection of the type of dosage form for a drug(9). Bioavailability enhancement by using lipid-based excipients could be attributed to one or more of the following mechanisms: solubility enhancement, safe carrier to the site of absorption, improve wetting, efflux inhibition, prevent crystallization, promote lymphatic uptake thereby bypassing the first-pass metabolism, prolong GI transit and reduce food effect. The majority of drugs approved for lipid-based drug delivery

belong to the self-emulsifying category. And hence the review would be focussing on the differences between various self-emulsifying systems excipients, methods of preparation, mechanisms, evaluation, and applications of those along with future challenges and opportunities for them.

SELF-EMULSIFYING SYSTEMS (SES) AND ITS TYPES

They are pre-concentrates or anhydrous form of emulsions which when introduced into an aqueous phase would form an emulsion under gentle agitation. SEDDS form an opaque o/w emulsion whereas SMEDDS and SNEDDS give rise to clear, transparent microemulsion with droplet sizes ranging from 10 – 250 nm. Key components of SES are the drug along varying proportions of oils, surfactants, and hydrophilic co-surfactants. In vivo, the agitation is provided by the peristaltic movement in the GIT. These formulations demonstrate high stability as well as generation of very large surface area due to small droplet sizes formed on dispersion which leads to an overall improvement in bioavailability by solubility enhancement(12). Major differences between the 3 systems are depicted in Table 2

Advantages of SES

a) Storage: These systems are thermodynamically stable and can be stored under a wide range of storage condition
b) Stability: SES is chemically and physically stable which in no less proportion can be attributed to the absence of water from the formulation.
c) Palatability and patient compliance: SES can be formulated into a variety of dosage form thereby helping in masking bad taste as well as the obnoxious odour of the drug as well as the excipients very effectively.
d) Food effects: The presence of GI contents has no significant effect on the dissolution and eventual absorption of the drug. Instead of the contents of SES aid in the dissolution of the drug.
e) The quick onset of action: The system instantaneously disperses in the GI milieu into very fine droplets. This aids in fast absorption and shows a quick onset of action.
f) Manufacturing versatility and ease of scale-up: Due to the relatively few excipients, simple processes and basic manufacturing equipment requirement makes SES very easy to scale up and manufacture on the large scale.

Pitfalls of SES

a) Drug precipitation: Ions, pH, and enzymes in the GI fluids can cause the drug to precipitate thereby overcoming the possible advantages offered by the system. Though this could be a problem this can be prevented by adding precipitation enhancers in the formulation.
b) The dilution effect on solvents can instigate precipitation of drugs. This could be overcome by the addition of polymers.
c) Co-solvents can vaporize via the capsule shell causing the drug to precipitate in vitro. This can be overcome by converting liquid systems into a solid one.
d) Liquid SES is relatively difficult to store, transport, and handle as compared to solid SES.
e) Lipophilicity and triglyceride solubility of the drug in correlation with lymphatic transport needs to be completely understood and a more adequate predictive model is required.
f) Lack of good predictive in vitro models for the assessment of the formulations
g) Peroxidation of unsaturated lipid material may lead to chemical and physical instability issues.
h) Liquid SES are relatively unstable due to microbial degradation.
i) Quality control tests for SES is cumbersome and exhaustive.
j) A higher concentration of surfactant in the formulation causes GI irritation.
k) Interaction of liquid or semi-solid SES preparation with excipients of soft gelatine capsules on a long period of storage
l) Polymorphism associated with thermo-softening lipid excipients can happen which needed to be controlled during manufacturing.

COMPONENTS OF SES

An ideal SES should have the following characteristics:

- The least possible volume of excipients should be used to solubilize the therapeutic amount of the drug.
- A shelf-life of a minimum of 2 years overall anticipated conditions
- Excipients used should have the GRAS status and should be used within acceptable limits.
- Ease of dispersion in the GI milieu without causing precipitation of drug.
- The dispersion should manipulate the digestion to process to enhance or maintain drug dissolution.
- It should promote the absorption of the drug via intestinal cells.

Drug

It is evident that SES would offer advantages for the formulation of drugs possessing inherently low

solubility i.e., BCS class II and class IV drugs. But that is not the case. Each class of drugs is afflicted by its own set of shortcomings. Bioavailability of BCS class I, III, and IV molecules maybe affected detrimentally by biotransformation and gut wall efflux(13). SES offers obvious solutions to the aforementioned issues. The formulation feasibility of a drug into an SES depends on the solubility of the drug in various excipients as well as the partition coefficient of the drug. A log P value of the drug between > 4 is recommended(14). Molecular weight isn't a property of relevance while deciding to pursue SES as a review of the literature reveals those drugs with molecular weight as low as 144 Da (valproic acid) to as high as 1202.64 Da (cyclosporine) have been formulated as SES.

The possible mechanism by which SES can improve the bioavailability of drugs can be depicted in Figure 1 which has been taken with permission from a review by Ghadi and Dand(13)

Excipients

Choice of excipients for the formulation of SES could be done based on its solvent capacity, miscibility with other ingredients to ensure stability and drug homogeneity, irritancy and toxicity, melting range, self-dispersibility, digestibility and fate of products of digestion, compatibility with excipients of the final formulation, purity, chemical stability and lastly cost(15)

Lipids

Lipids are at the very heart of an SES formulation. SES is generally made up of drugs suspended or preferably dissolved in oils; which could be long-chain, middle chain, or its combination. The biggest advantage of using oil is that lipophilic drugs are pre-dissolved thereby rendering dissolution of the drug within the GI tract, not a rate-limiting step. During the digestion process, they attract endogenous surfactants like bile salts and phospholipids which allow micellization of drugs and ensure their dissolved state in vivo(16). Mono- and diglycerides or mixed glycerides normally exhibit better solvent ability as compared to triglycerides without losing any of the digestion advantages offered by triglycerides. Their amphiphilicity may demonstrate improved emulsification. They also offer better miscibility with surfactants. Another way of classifying oils is based on chain length. Long-chain fatty acids typically have lower solvent capacity and poor emulsification potential as compared to medium-chain fatty acids. They are also more prone to oxidative degradation but on other hand promote lymphatic uptake of lipophilic drugs. Glycerides used could be saturated or unsaturated. Unsaturated glycerides are normally liquid at room temperature and are superior to saturated glycerides with respect to solvent capacity and lymphatic uptake but they are prone to rancidity due to epoxidation of unsaturated bonds in presence of oxygen(17). Novel semi-synthetic medium-chain glycerides, which are amphiphilic compounds with emulsifier properties, are gradually replacing the regular medium-chain triglyceride oils in the formulation of SES(18). Table 3 lists out the class of lipids that could be used to formulate SES.

Some brands of oils which have found widespread application in the preparation of SES are Labrafac CC, isopropyl myristate, Capmul MCM, Maisine 35-1, Akoline MCM, Capmul MCM C-8, Capmul GMS-50K, Labrafil M 1944 CS, Brij, Stepan GDL, Caprol ET, Labrafac 1349, Labrafac PG, Labrasol, Lauroglycol 90, etc

Surfactants

Surfactants are the ones on whom the success of the system depends majorly. Various properties of a surfactant such as the HLB value, cloud point, viscosity, etc which could affect the emulsification process. The concentration of surfactants is has a direct bearing on the droplet size(19) but it could swing in either direction. In some cases increase in the concentration of the surfactant leads to a decrease in droplet size which could be because of the stabilization of the oil-water interface due to the insertion and localization of surfactant molecules (20). In some instances, increasing the concentration of surfactants has led to an increase in the droplet size which could be attributed to high surfactant concentration leading to permeation of water into oil droplets leading to disruption of the interface rather than stabilization. Hence judicious use of surfactants is important for the development of a stable and successful SES as the least possible particle size is essential to provide maximum area for absorption(21). Other than these surfactants contribute to increase in the bioavailability of drugs due to reasons such as improved drug dissolution, reduce the tight junction permeability, and inhibition of efflux based cellular excretion. HLB on the higher side and hydrophilic nature are preferable for the instantaneous formation of minute emulsion droplets which spreads equally rapidly in the aqueous environment of the GIT. Emulsifiers normally used at the prescribed concentration(30 – 60%) are largely safe but are known to show certain side effects like irritation to the mucosa, vomiting, abdominal pain, flatulence and diarrhoea(22). Generally single alkyl chains are

more penetrative, hence surfactants such as polysorbates and triglyceride ethoxylates are concluded to be less toxic.

The digestion of surfactants has shown to have an impact on the performance of SES. This is because its digestion can change the environment of the drug, which in turn can cause precipitation of the poorly water-soluble drugs(23). Although thus far very little is known about the products formed after the digestion of surfactants and their supposed interactions with fatty acids, bile salts, phospholipids, and dietary lipids but it is purported that that may have a negative effect on the solubility of drug(24). All of these findings make one thing apparent that inhibition of triglyceride digestion by non-ionic surfactants makes it the foundation stone for the development of SES(12).

Natural emulsifiers are generally considered safer than synthetic ones and have now been explored in the formulation of SES. Odeberg and his team have successfully used galactolipids which are polar lipids found in the chloroplast membrane of plants as surfactants to develop SEDDS of cyclosporine. They were able to produce a formulation with absorption characteristics almost identical to the commercially available Sandimmune Neoral® as they could confirm by clinical trials(25). Nonetheless, such surfactants of natural origin usually are limited by their self-emulsification capacity.
Some of the common emulsifiers used are given in Table 4

Co-surfactants/ co-solvents
As previously discussed, we can recognize that hydrophilic surfactants in very high concentrations are required to formulate SES. Co-solvents like ethanol, propylene glycol, polyethylene glycol, etc are used to solubilize them. These at times can act as co-surfactants to form microemulsion(12). They also help in relieving the stress at the oil-water interface by allowing it to be flexible enough to take up various curvatures over a wide concentration range. The only drawback is that these solvents may get evaporated via the capsule shell in which the SES has been filled and that would lead to precipitation of the drug(26).
Some commonly used co-solvents are Span 20, Span 80, Caproyl 90, polyethylene glycol, ethanol, lauroglycol, isopropyl alcohol, etc(27).

Antioxidants
Maintaining adequate chemical and physical stability of SES is challenging. As already reviewed(17), unsaturated lipid excipients can undergo peroxidation. This can be minimized by the incorporation of saturated medium-chain (C6-C12) triglycerides found in coconut or palm kernel oil like caproic acid (C6), caprylic acid (C8), capric acid (C10), or lauric acid (C12) and by use of appropriate antioxidants. Phenol-based antioxidants such as Vitamin E (α-tocopherol), butylated hydroxytoluene (BHT), butylated hydroxy anisole (BHA), and propyl gallate can act synergistically with oxygen scavengers such as ascorbic acid and its lipid-soluble counterpart, ascorbyl palmitate.

Precipitation inhibitors
Super saturable formulations allow drugs to reach the GIT at a concentration greater than their equilibrium solubility. These high concentrations provide the greatest flux and promote the absorption of drugs(28). SES are excellent candidates to be manufactured as supersaturated formulations as they allow the drug's solubility to increase above its equilibrium solubility by incorporation of surfactants and co-solvents/ co-surfactants. But these systems would be thermodynamically unstable and would cause the drug to precipitate rapidly in vivo thereby leading to a reduction in bioavailability. In vivo drug precipitation may occur due to sudden pH change, dilution of formulation with GI fluids, and digestion of the solubilizing excipients in the formulations(29). Supersaturation must be generated and maintained for the desired time frame. Thus, it is important to consider this while formulating a super saturable formulation to prevent any problems during the absorption of the drug. The concept of creation and maintenance of a supersaturated state could be effectively explained by the "Spring and Parachute" theory(30). The theory states that a thermodynamically unstable, supersaturated solution of a drug is usually generated from a higher energy form of the drug i.e., "a spring" and to take maximum advantage of this supersaturated state it needs to be prolonged for a long period by use of precipitation inhibitors i.e., "the parachute". Several precipitation enhancers have been reviewed in the literature and have been found to be effective by various researchers(31). They include cellulosic polymers like hydroxypropyl methylcellulose (HPMC), vinyl polymers like polyvinyl alcohol, Poly (vinyl acetate)-co-poly/vinylpyrrolidone), Soluplus®, surfactants like Poloxamer 407 multigraft copolymer and cyclodextrins. They normally act by interfering with nucleation or crystal growth thereby retarding precipitation of drugs. They reduce precipitation by manipulating hydrogen bonding, hydrophobic interactions, steric hindrance, and polymer rigidity. A significant

increase in oral bioavailability with supersaturated SES has been reported for several poorly water-soluble drugs including halofantrine(32), albendazole(33), lovastatin(34), and fenofibrate(35).

Aqueous phase

Per se water isn't a formulation ingredient but we have included it under this section to highlight the fact that the success of SES depends not just on the excipients and manufacturing processes used but also on the nature of the aqueous phase where those might be introduced. The pH, ionic content and enzymes present contribute significantly to the behaviour of these systems in vivo. In the GIT the systems would experience a wide range of pH as well as various ions which can make the formulation behave unexpectedly. Even the enzymes may digest the formulation ingredients into products which may bring about changes that might defeat the purpose of the formulation. Thus, it is advisable to test the behaviour of SES in all possible scenarios to be prepared for any eventuality. The characteristics to be checked could include self-emulsibility, droplet sizes, and precipitation of drugs. To check these various mediums covering the entire bouquet of situations could be used. Some recommended media are plain water, Ringer's solution, simulated gastric fluid (pH 1.2), simulated intestinal fluid (pH 6.8), and phosphate buffer saline. This kind of evaluation becomes even more required if the drug in the formulation demonstrates a pH-dependent solubility.

A lot of literature about the mechanism of self-emulsification, preparation, and evaluation of these systems is already available and hence is not included in the scope of this article as this one predominantly focuses on the versatility of SES.

CONVERTING THE SES INTO THE FINAL DRUG DELIVERY SYSTEM

Upon successful preparation and evaluation of SES, the next main challenge is to make it available to the patients conveniently and acceptably. For obvious reasons oral route remains the most popular one and hence a very percentage of all formulated SES target the oral route. But other routes of drug administration have also been explored for the delivery of SES. The next part of the review would focus on converting the prepared SES into a form that would be readily acceptable by the patient and is also able to maintain the physical and chemical stability of the prepared SES. These systems could be incorporated into the final dosage form in 3 states. First of which is the original liquid state or by use of certain surfactants which would increase the viscosity to a semisolid phase and lastly by converting it into a solid form using any suitable technique.

Liquid SES

Conventional SES are liquid in nature and are mostly supplied as soft gelatine capsules. But these have myriad of limitations like high production cost, low portability, low drug loading, evaporation of co-solvents via the shell leading to precipitation of drug, hang-up during swallowing(36). But all things considered a very large number of molecules have been formulated as liquid SEDDS, SMEDDS and SNEDDS. Some of the molecules that have been formulated as liquid SES are etoposide(37), puerarin(38), carvedilol(26), tacrolimus(39), cyclosporine(40) to name a few.

Semisolid SES

The semisolid SES are formed using similar lipidic constituents as those used for the liquid SES, but with a melting point above room temperature. Such formulations do not need any co-surfactants/ co-solvents. These formulations exhibit viscosity higher than the parent liquid SES and thus provide improved drug stability and better handling properties. However, as expected, under in vivo conditions, these formulations tend to suffer from poor emulsification efficiency due to the presence of high melting point lipids, potentially leading to inconsistent drug absorption and variable bioavailability(41). Lauryl macrogol-glycerides such as Gelucire 44/14, Gelucire 50/13, polyoxyethylene hydrogenated castor oil derivatives such as Nikkol HCO50, cetyl alcohol derivative (e.g., Emulcire 61WL), and polyoxyethylene polyoxypropylene block polymer (e.g., Lutrol F127, Lutrol F188) are the commonly employed excipients for the preparation of semisolid SES. Semisolid SEDDS of valsartan(42), acyclovir(43), carvedilol(26) and atorvastatin(44) have been reported in the literature.

Solid SES (S-SES)

SES was most popular in their liquid state. But they show some limitations, for example, low stability, irreversible drugs/excipients precipitation, a large volume of dose, difficulty to handle, and few choices of dosage forms to dispense to patients. These could all be addressed by converting liquid SES into solid SES. This conversion doesn't affect the in vivo behaviour of the system but helps in overcoming the aforementioned drawbacks. Thus, they can benefit from the best of both worlds and offer a lot more dosage form options and drug release patterns to a formulation scientist. They can

give combined benefits of excellent solubility and bioavailable offered by liquid systems along with high stability, reproducibility, compactness of dosage form, ease of handling, and overall better patient compliance that comes along with the use of a solid unit dosage form(45). Solid SES are being developed from liquid/semisolid SES mainly by adsorption on solid carriers(46), spray drying(47), lyophilization(48), fluidized bed drying (49), melt granulation(50), melt extrusion(51), and nanoparticle technology. Though solidification can prove to be advantageous it comes with its own set of problems such as:

- The number of solidifying excipients may affect the release of the drug
- The amount of solidifying excipients may affect the release of the drug
- Probability of irreversible phase separation on reconstitution
- Clogging of spray nozzles due to oil content in the spray drying method
- Degradation of the drug during the solidification process
- Reduction in drug loading capacity
- Difficulty in ensuring content uniformity
- Probability of residual solvents used during granulation.

Different researchers have explored the realm of formulation design and have converted these SES in either state into a stable and effective formulation. Thereby they could attain better targetability, bioavailability, control on drug release profiles, and intended pharmacokinetic profile. Table 5 gives a list of the plethora of forms in which these SES have been envisaged.

CONCLUSION

High throughput screening and combinatorial chemistry are excellent tools for the development of new drugs but the trend shows that the drugs coming out of those would be afflicted by poor solubility and low bioavailability. This would be an extremely tough challenge for a formulation scientist. Though a lot of options are available but lipid-based systems do provide a very good alternative to enhance the bioavailability of lipophilic molecules. In that, self-emulsifying systems provide one of the best options to overcome the problem. These systems are capable of bioavailability enhancement not just by improving solubility but they also help in better penetration through biological membranes, bypass the first-pass metabolism by lymphatic uptake and prevent the P-gp efflux from getting activated. Other than the drug these systems have 3 basic components – lipids, surfactants, and co-surfactants/ co-solvents. The popularity of these systems is evident from the number of research articles and patents on the said topics. Not just that a lot of products have already found approval and are beings used commercially. The preparation of these systems, as well as its evaluation, doesn't have any special requirements making them ready for scale-up. The development of these systems, on the other hand, is a Herculean task. Right from the screening of the right blend of excipients to the cumbersome in vitro as well as in vivo testing and finally, stability testing makes their development challenging with a fruitful end. The conventional systems which are liquid in nature have shown a problem of drug precipitation both in vitro and in the GIT. This can be overcome quite effectively by converting those liquid formulations into semisolid or solid ones. Another approach to solving this was to use polymers and precipitation enhancers.

These systems are versatile not just in the choice of excipients, the state in which they could be manufactured but even in the abundance of dosage form choices in which they can be easily incorporated. The review must have given researchers the various dosage forms that have been tried, some of which have been used extensively whereas some are just finding their footing. Though these systems have been around for over 30 years but its validity and usefulness hasn't been explored completely. Research teams are working on developing nutraceuticals, cosmeceuticals, and herbal medicines. A few teams have also tried to use these to deliver biologics like peptides, genetic material, enzymes, etc. Diseases that they have been used to treat range from infections, metabolic disorders to even cancer. One of the inherent causes of worry while using these systems chronically is the toxicities due to surfactants. Galactolipids based as well as biosurfactants are being explored to be used to make these systems at par as that made by using synthetic surfactants. To amplify their already available benefits techniques like super saturable SES, cationic SES, polar lipid-based SES and self-double emulsifying drug delivery systems are finding some application. Researchers have also started working on adapting these systems for 3D-printing applications to bring in more personalization. Thus, this review does recount all that is done but also points out the areas where lacunae exist and also highlights newer research that could be carried out in the field of "selfies".

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TABLE 1: THE LIPID FORMULATION CLASSIFICATION SCHEME (LFCS) SHOWING INDIVIDUAL PERFORMANCE CHARACTERISTICS

LFCS class	I	II	IIIA	IIIB	IV
Type of formulation	Oily solution	SEDDS without a water-soluble component	SEDDS/ SMEDDS with a water-soluble component	SMEDDS or SNEDDS with water-soluble components and a low oil content	Oil-free or micellar formulation consisting of surfactants and co-solvents
% w/w of oils	100	40 – 80	40 – 80	< 20	-
% w/w of water insoluble surfactants	-	20 – 60	-	-	0 – 20
% w/w of water-soluble surfactants	-	-	20 – 40	20 – 50	30 – 80
% w/w of co-solvents	-	-	0 – 40	20 – 50	0 – 50
Initial solvent capacity	Poor	Intermediate	Slightly above intermediate	High	High
Dispersion type formed	Limited or no dispersion	Emulsion	Micro- or nano emulsion	Micro- or nano emulsion	Micellar solution
Solvent capacity upon dispersion	No impact	No impact	Possible loss	Possible loss	Likely loss
Digestion requirement	Required digestion	Likely to be digested	Digestion may not be necessary	Digestion may not be necessary	Least digestible
Solvent capacity upon digestion	Increased	Possible loss	Possible loss	Possible loss	No impact
Type of phase diagram	-	Ternary phase diagram needed	Pseudo ternary phase diagram	Pseudo ternary phase diagram	-
Precipitation inhibitors	Not required	Not required	Recommended	Recommended	Recommended
Droplet size	Coarse	250 nm – 5 µ	100 – 250 nm	50 – 100 nm	< 50 nm
Marketed preparation	Avodart®, Amitiza®, Rocaltrol®	One-Alpha®, Sandimmune®	Norvir® (Discontinued)	Neoral®	Agenerase®,

TABLE 2: DIFFERENCES BETWEEN SEDDS, SMEDDS AND SNEDDS

Criteria	SEDDS	SMEDDS	SNEDDS
Droplet size	250 nm – 5 µ	100 – 250 nm	50 – 100 nm
Appearance	Turbid or opaque	Optically transparent	Optically transparent
HLB of surfactants needed	$\leq$12	$\geq$12	>12
Class as per LFCS	Type II or IIIA	Type IIIA or IIIB	Type of IIIB
Concentration of oil used	40 – 80%	< 20%	< 20%
Concentration of total surfactants used	30 – 40%	40 – 80%	40 – 80%

TABLE 3: LIPIDS USED IN FORMULATION OF SES

Class	Examples
Fatty acids	Oleic acid, palmitic acid, stearic acid, linolenic acid
Long chain triglycerides	Corn oil, soybean oil, safflower oil, olive oil, peanut oil, sesame oil
Medium chain triglycerides	Glyceryl tricaprylate/ caprate
Propylene glycol esters	Propylene glycol monocaprylate, propylene glycol monolaurate
Monoglycerides and diglycerides	Glyceryl caprylate/ caprate, glycerol monocaprylate, glycerol monooleate

TABLE 4: COMMON SURFACTANTS USED IN FORMULATION OF SES

Category	Examples
Low HLB emulsifiers (HLB < 10)	
Phosphatidylcholine or Phosphatidylcholine-solvent mixtures	Phosphatidylcholine (HLB 7.5-8.5), phosphatidylcholine in propylene glycol, phosphatidylcholine in medium chain triglycerides, phosphatidylcholine in safflower oil, phosphatidylcholine in ethanol
Unsaturated polyglycolized glycerides	Oleoyl macrogol glycerides (HLB 3.5), linoleoyl macrogol glycerides (HLB 9)
Sorbitan esters	Sorbitan monooleate (HLB 4.3), sorbitan monostearate (HLB 4.7), sorbitan monolaurate (HLB 8.6), sorbitan monopalmitate (HLB 6.7)
High HLB emulsifiers (HLB>10)	
Polyoxyethylene sorbitan esters	Polysorbate 20 (HLB 16.7), polysorbate 40 (HLB 15.6), polysorbate 60 (HLB 14.9), polysorbate 80 (HLB 15)
Polyoxyl castor oil derivatives	Polyoxyl 35 castor oil (HLB 12-14), polyoxyl 40 hydrogenated castor oil (HLB 15)
Polyoxyethylene–polypropylene block copolymer	Poloxamer 188 (HLB 29), Poloxamer 407 (HLB 18)
Saturate polyglycolized glycerides	Lauroyl macrogol glycerides (HLB 14), stearoyl macrogol glycerides (HLB 13)
PEG-8 caprylic/ capric glycerides	Caprylocaproyl macrogol glycerides (HLB 12)
Vitamin E derivative	Tocopherol PEG succinate (HLB 13.2)

TABLE 5: LIST OF FORMULATIONS FOR DELIVERY OF LIQUID/ SEMISOLID/ SOLID SES

Type of formulation	Name of the drug
For Oral Delivery	
Powders	Lercanidipine(46), Ketoprofen(52)
Granules	Ondansetron(53), Ezetimibe(54)
Pellets	Diazepam(55), Nitrendipine(56)
Self-Emulsifying Controlled Release Tablets (SECRET)	Coenzyme Q10(57), Carvedilol(58)
Gastroretentive SEDDS	Tacrolimus(59), Tetrahydrocurcumin(60)
Osmotic SEDDS	Carvedilol(61), Cyclosporine A(62)
Microspheres	Furosemide(63), Loratidine(64)
Controlled Release Capsules	Ritonavir(65), Dexamethasone(65)
Hybrid Microparticles	Celecoxib(66), Telmisartan(67)
Nanoparticles	5-fluorouracil(68), Paclitaxel(69)
Mucoadhesive Systems	Cannabnoids(70)
Orally Dissolving Films	Vitamin D3(71), Indomethacin(72),
Colonic Minispheres	Cyclosporin A(73)
Carbon Nanotubes-Based SES	Erythropoietin(74)
Lipid Matrices	Antidepressants, Anxiolytics, Antiemetics, and Galenicals(75)
SES Loaded Sponges	Curcumin(76), Paclitaxel(77)
For Non-Oral Delivery	
Suppositories	β-Artemether(78), Indomethacin(79)
Implants	Carmustine(80)
Transdermal Systems	Indomethacin(81), Curcumin(82)
Ocular Systems	Indomethacin(83), Acyclovir(84)
Injections	Docetaxel(85,86), Paclitaxel(87)
Nasal Systems	Dimenhydrinate(88)
Vaginal Systems	Curcumin(89)
Pulmonary Systems	Amikacin(90)
3D Printed Solid SES	Fenofibrate(91), Cinnarizine(91)

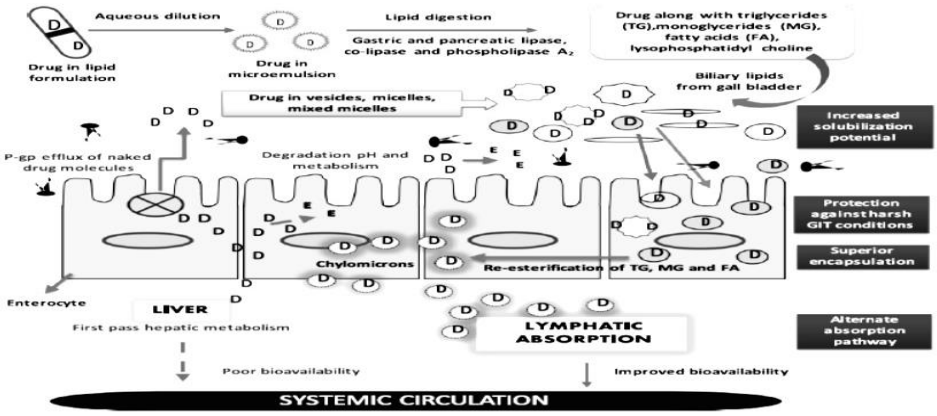

Fig. 1: *Mechanisms and advantages associated with SES*