Chapter

Self-Emulsifying Drug Delivery Systems: Easy to Prepare Multifunctional Vectors for Efficient Oral Delivery

Khaled AboulFotouh, Ayat A. Allam and Mahmoud El-Badry

Abstract

Self-emulsifying drug delivery systems (SEDDS) have been mainly investigated to enhance the oral bioavailability of drugs belonging to class II of the Biopharmaceutics Classification System. However, in the past few years, they have shown promising outcomes in the oral delivery of various types of therapeutic agents. In this chapter, we discuss the recent progress in the application of SEDDS for oral delivery of protein therapeutics and genetic materials. The role of SEDDS in enhancing the oral bioavailability of P-glycoprotein and cytochrome P450 3A4 substrate drugs is also highlighted. Also, we discuss the most critical evaluation criteria of SEDDS. Additionally, we summarize various solidification techniques employed to transform liquid SEDDS to the more stable solid self-emulsifying drug delivery systems (s-SEDDS) that are associated with high patient compliance. This chapter provides a comprehensive approach to develop high utility SEDDS and their further transformation into s-SEDDS.

Keywords: solid self-emulsifying drug delivery systems, solidification techniques, oral delivery, P-glycoprotein (P-gp), cytochrome P450 3A4 (CYP3A4), multidrug resistance (MDR), protein therapeutics, plasmid DNA (pDNA)

1. Introduction

Lipid-based drug delivery systems (LBDDs) have been intensively investigated to overcome various obstacles encountered in oral drug delivery including poor aqueous solubility, limited permeability, low therapeutic window, first pass metabolism as well as inter- and intraindividual variability in drug response [1]. Lipid-based nanoparticles can achieve high loading capacity of hydrophilic and hydrophobic drugs [2]. The delivery features of these drug delivery systems could be tailored to achieve either immediate or sustained release properties depending on the appropriate selection of lipid composition. Most of lipids employed in the formulation are generally recognized as safe (GRAS), biocompatible and biodegradable [3]. LBDDs can enhance both transcellular and paracellular transport of drugs by transient disruption of lipid bilayer cells and alteration of tight junction by products of lipid digestion, respectively. Interestingly, they could permeate challenging physiological barriers such as blood brain barrier without surface

modification due to their lipophilic nature [4]. Further, they are promising carriers for protection of therapeutic peptides against harsh GI environment [3]. Ease of preparation, cost effectiveness and possibility of large-scale production make LBDDs more attractive compared to polymeric nanoparticulate delivery systems [5].

2. Classification of lipid carriers

Lipid carriers can be classified into various categories depending mainly on their method of preparation as well as their physicochemical properties. They include liposomes, niosomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), micro and nanoemulsions, self-emulsifying drug delivery systems (SEDDS), and lipid-drug conjugates [2, 4].

Liposomes are uni- or multilamellar spherical vesicles which are composed of cholesterol and other natural or synthetic phospholipids enfolding an aqueous compartment [6]. They were first introduced by Bangham et al. in 1965 [7]. Thus, liposomes have been considered as biocompatible and biodegradable carriers that possess efficient delivering capability of hydrophilic and hydrophobic drugs. Advantages of liposome-based drug delivery systems include reduction of systemic and of target toxicities as well as targeting potential to achieve the desired outcome [8]. Thus, many liposome formulations have been approved for commercial use such Ambisome® (amphotericin B), Depocyt® (cytarabine), DepoDur® (morphine sulfate) and many others. However, their poor stability and rapid elimination by reticuloendothelial system limit the widespread applicability of liposomal formulations [4].

Niosomes are first described by Handjani-Vila et al. in 1979 [9]. They are nonionic surfactant-based vesicles in which the hydrophilic surfactant heads are oriented toward the exterior and the interior of the bilayer while, the hydrophobic tails are enclosed inside the bilayer. Therefore, like liposomes, niosomes have the ability to encapsulate hydrophilic or lipophilic molecules [10]. Niosomes also have cholesterol in their structure which enhances the rigidity of bilayer and reduces premature drug release [11]. Niosomes are superior carriers to liposomes in terms of production cost, chemical and physical stability, and loading capacity [12].

SLNs and NLCs are the most widely described solid-core lipid-based nanocarriers in the scientific literature [3]. SLNs were first described in 1991 to replace the liquid oil of O/W emulsions by a single solid lipid or mixture of solid lipids [2]. SLNs are composed of either solid lipid or mixture of lipids, that do not melt at room or physiological temperature, in an aqueous dispersion stabilized with the help of nonionic surfactants [3].SLNs offer the advantage of avoiding the use of organic solvents during preparation, effective delivery of both hydrophilic and lipophilic drugs, feasibility of surface functionalization with specific moieties to enhance their targeting potential, possibility of extended or controlled drug release, long shelf-life, biocompatibility, lower acute or chronic toxicity and effective large-scale production [2, 13, 14]. On the other hand, efficient drug delivery by SLNs is challenged by low drug loading capacity due to lipid crystalline nature, expulsion of loaded drug due to perfect crystalline lattice formation of the lipid and erratic gelation tendency that results in particle aggregation during storage [4, 14].

NLCs were developed to overcome the problem of drug expulsion during phase transition or crystallization of lipids comprising SLNs [15]. They also exist as a solid lipid matrix at temperature up to about 40°C. However, they are composed of solid lipid mixed with an oil which in turn reduces the lipid crystallization capacity and enhances the drug loading efficiency [16].

Nanoemulsions are kinetically stable heterogeneous systems composed of ultrafine oil droplets dispersed in aqueous media and stabilized by the aid of surfactants

and cosurfactants. Nanoemulsions have gained increasing attention as promising drug delivery systems due to their multiple advantages including high surface area for drug absorption, biocompatibility, increasing drug solubility and improving mucosal permeability. Further, many FDA approved nanoemulsion-based products of water insoluble drugs are now available for clinical use including Restasis®, Estrasorb® and Flexogan®. Microemulsions also offer favorable characteristics such as thermodynamic stability, ease of production being formed spontaneously without the need for high energy input and high penetration due to the large surface area of internal phase [17].

Lipid-drug conjugates (LDCs) are lipid nanoparticle formulations which are characterized by the conjugation ability of the lipid matrix with the hydrophilic drug moieties, and thus provide novel pro-drugs to achieve many therapeutic outcomes in oral drug delivery [18]. Like other lipid-based nanocarrier systems, LDCs possess several advantages including biocompatibility, being solid at body and room temperature, high capacity for loading hydrophilic drugs, high permeation through GI tract, enhanced drug absorption through lymphatic uptake, improving stability and bioavailability loaded drugs, and feasibility of large scale production [19].

3. Self-emulsifying drug delivery systems

Self-emulsifying drug delivery systems (SEDDS) are lipid-based formulations that encompass isotropic mixtures of natural or synthetic oils, solid or liquid surfactants and co-surfactants [20]. When they are exposed to aqueous media (e.g., gastrointestinal fluids), they undergo self-emulsification to form O/W nanoemulsions or microemulsions with a mean droplet size between 20 and 200 nm [21]. Consequently, SEDDS are usually referred to as self-nanoemulsifying drug delivery systems (SNEDDS) or self-microemulsifying drug delivery systems (SMEDDS) depending on the nature of the resulting dispersions formed following their dilution [20].

SEDDS have been reported to enhance the oral bioavailability of poorly water-soluble drugs particularly those belonging to class II of the Biopharmaceutics Classification System by multiple underlying mechanisms [22]. Among these mechanisms, the enhanced drug solubilization was the most widely investigated. Lipidic components of SEDDS stimulate lipoprotein/chylomicron production thus promoting drug absorption [23]. The ultrafine droplet size range of the resulting emulsion provides a large surface area of interaction with gastrointestinal (GI) membranes [24]. Importantly, the bioactive effects of various ingredients employed in SEDDS formulation have significantly contributed to the enhanced oral bioavailability of the loaded drugs. These bioactive effects include tight junction opening and increasing membrane fluidity by the high surfactant content employed in SEDDS formulation [25]. Furthermore, stimulation of the intestinal lymphatic pathway as well as inhibition of intestinal drug efflux pumps such as P-glycoprotein (P-gp) and intestinal cytochrome P450 3A4 (CYP3A4) are considered promising strategies for enhancing the oral delivery of P-gp substrates and bypassing intestinal and hepatic first pass metabolism [26].

P-gp is an energy-dependent membrane bound protein and the most abundantly distributed ATP-binding cassette transmembrane transporter throughout the body [27]. P-gp prevents the accumulation of endogenous substances and xenobiotics in cells by transporting them back to the extracellular space [28]. Unfortunately, intestinal P-gp transporters hamper the intestinal uptake of substrate drugs thus, reducing their oral bioavailability. Additionally, overexpression of P-gp transporters is involved in the development of multidrug resistance (MDR) in numerous human tumor types [29]. Hence, many strategies have been developed to inhibit P-gp

activity for enhancing the oral bioavailability of P-gp substrate drugs and reversing MDR in tumor cells. Among these strategies, nanocarriers have been widely investigated [26]. Nanocarriers have the advantage of protecting P-gp substrates against premature release and interaction with the biological environment [30]. They control drug tissue distribution and favorably accumulate in tumor tissue [31, 32]. Among various nanocarriers, SEDDS have been widely explored to enhance the oral bioavailability of P-gp substrate drugs and reverse MDR in tumor cells.

Interestingly, the unique combination of SEDDS properties allows the enhancement of oral bioavailability of both hydrophobic and hydrophilic drugs [33]. The oral delivery of protein therapeutics and genetic materials represents a real challenge due to their hydrophilic nature and their large molecular weight. In this chapter, we discuss the recent progress in the application of SEDDS for enhancing the oral bioavailability of P-gp substrates, reversing MDR in tumor cells and oral delivery of protein therapeutics and genetic materials. The aim of the current discussion is to call attention to the unique combination of SEDDS properties that makes them multifunctional delivery systems acting *via* various mechanisms to enhance the oral delivery of target therapeutic agents.

3.1 SEDDS overcome P-gp-mediated efflux and reverse MDR in tumor cells

Over the past 2 decades, SEDDS have been widely investigated to overcome P-gp-mediated efflux of substrate drugs to enhance their oral bioavailability. The potential of SEDDS to inhibit P-gp activity relies mainly on the excipients with established P-gp inhibition activity that are employed in the formulation [26]. Nonionic surfactants are the most widely employed excipients and are considered the mainstays of P-gp inhibition by SEDDS [29]. Cremophor EL, Cremophor RH40, vitamin E TPGS 1000, Labrasol, Transcutol P and Tween 80 are the most frequently employed. P-gp inhibition activity of a given surfactant depends on its HLB value and the structure of its hydrophobic domain [34]. There is no obvious correlation between surfactants' HLB values and P-gp inhibition activity. Structurally, the hydrophobic moieties of the surfactant should be linked to polyoxyethylene hydrophilic side chains to inhibit P-gp activity [34].

The binding affinity of nonionic surfactants to the hydrophobic portion of P-gp molecule is different from that of ionic surfactants [35]. Nonionic surfactants can change the secondary or tertiary structure of P-gp molecule resulting in the loss of its function [36]. Additionally, non-ionic surfactants were reported to modulate P-gp activity by inhibiting P-gp ATPase activity and either membrane fluidization or rigidization [37, 38]. At concentrations below the critical micelle concentration, nonionic surfactants are most effective in reducing P-gp activity; however, surfactant micelles showed some P-gp modulation activity [26].

SEDDS have superior formulation efficiency and *in vivo* performance compared to their individual components [39]. Various formulation aspects of SEDDS can potentiate the P-gp inhibition activity of their ingredients. The entrapment of P-gp substrate within the ultrafine emulsion droplets provides a protection against recognition by P-gp efflux pumps at GI epithelium [33]. In addition, SEDDS allow the co-administration of several excipients which are co-localized in close proximity to GI epithelium [22]. Further, pharmaceutical excipients with established P-gp inhibition activity (e.g., curcumin) or traditional P-gp inhibitors (e.g., elacridar) could be loaded into the SEDDS formulation to further augment their P-gp inhibition activity [40, 41].

On the other hand, the efflux of chemotherapeutic agents by P-gp transporters, which are overexpressed in tumor cells, represents a major obstacle in cancer chemotherapy [42]. SEDDS are extensively investigated to overcome MDR in tumor

cells which is partly attributed to the overexpression of P-gp efflux transporters. SEDDS allow the combinational delivery of multiple chemotherapeutic agents acting *via* independent pathways in the same vector to produce a synergistic anticancer activity [42]. Interestingly, SEDDS could be employed for the co-delivery of various antioxidants for overcoming the oxidative stress in cancer cells [43].

3.2 SEDDS enhance the oral delivery of protein and peptide therapeutics

Protein therapeutics have a significant role in almost every field of medicine. However, the extensive application of protein therapeutics is challenged by their route of administration, being administered by parenteral route which is associated with reduced patient compliance [44]. Consequently, there is a great interest in the development of noninvasive strategies for delivery of protein therapeutics [45]. Oral delivery systems have been extensively investigated for the administration of protein drugs [46]. Unfortunately, the oral delivery of protein and/or peptide therapeutics is challenged by several barriers including the acidic environment

Protein	SEDDS composition	Bioavailability increase	Control	Animal species	Ref.
β-lactamase	Lauroglycol FCC (41.7%) Cremophor EL (33.3%) Transcutol HP (25%)	1.29-fold	β-lactamase solution	Sprague–Dawley rats	[54]
Insulin	Miglyol 840 (65%) Cremophor EL (25%) Co-solvent (DMSO and glycerol, 1:3) (10%)	3.33-fold	Insulin solution	Sprague–Dawley rats	[55]
Insulin	Ethyl oleate (35%) Cremophor El (32.5%) Alcohol (32.5%)	6.5-fold	Insulin solution	Male Wistar rats	[56]
Leuprorelin	Capmul MCM (30%) Cremophor EL (30%) Propylene glycol (10%) Captex 355 (30%)	17.2-fold	Leuprolide acetate solution	Sprague-Dawley rats	[57]
Pidotimod†	**Oil phase:** SoyPC (9.6%) Span 80 (21.1%) Oleic acid (36.1%) MCT (12%) 0.5% gelatin solution (3%) H_2O (12%) **Surfactant phase:** Tween 80 (6%)	2.56-fold	Pidotimod solution	Sprague–Dawley rats	[48]
Enoxaparin	Captex 8000 (30%) Capmul MCM (30%) Cremophor El (30%) Propylene glycol (10%)	2.25%■	Enoxaparin IV solution	Sprague-Dawley rats	[58]
	Labrafil 1944 (35%) Capmul PG 8 (25%) Cremophor EL (30%) Propylene glycol (10%)	2.02%■			

Abbreviations: DMSO, dimethyl sulfoxide; MCT, medium chain triglycerides.
■*Absolute bioavailability.*
†*Self -double emulsifying drug delivery system.*

Table 1.
SEDDS-mediated enhancement in the oral bioavailability of various proteins. Reprinted with permission from Ref. [33] © Elsevier (2018).

in the stomach, degradation by GI enzymes, mucus barrier as well as low cellular penetration [47]. Several strategies have been developed to overcome these barriers [48–50]. As shown in **Table 1**, SEDDS have been extensively investigated as promising carriers for oral delivery of protein and peptide therapeutics. Various surfactants and oils that are employed in SEDDS formulation have a permeation enhancing effects; thus, they increase the cellular uptake of hydrophilic macromolecules such as protein therapeutics. The ultrafine droplet size provides a large surface area for rapid intestinal permeability. The anhydrous nature of SEDDS protects proteins against aqueous hydrolysis. Other bioactive effects of SEDDS such as tight junction opening, and enhanced lymphatic uptake also contribute to the enhanced oral bioavailability of loaded protein therapeutics [49]. However, loading of protein therapeutics into SEDDS is challenged by their hydrophilic nature. Thus, the lipid solubility of protein therapeutic should be increased before their incorporation into the SEDDS preconcentrate. This could be achieved by various techniques including, hydrophobic ion pairing [51], double emulsification [48], using hydrophilic solvents or co-solvents [52] and chemical modification of the peptide molecule [53].

Figure 1 summarizes various hypotheses for the enhanced oral delivery of protein and peptide therapeutics by SEDDS. Protein therapeutics incorporated within the ultrafine oil droplets are effectively protected against degradation by GI enzymes. Further, these cargoes are absorbed when the nanosized oil droplets are absorbed. Thus, the protection against enzymatic degradation is achieved *via* controlling the release rate of loaded protein therapeutic [59]. Burst release could result in rapid degradation of protein molecules within the GI lumen before reaching the absorption site [60]. Another suggested mechanism for the enhanced oral bioavailability by protein therapeutics incorporated in SEDDS is based on the bioactive effects of SEDDS ingredients. They include mucus penetration, enhanced paracellular transport *via* opening of tight junction, and enhanced cellular uptake by transcytosis-mediated transcellular transport [61, 62]. Finally, enhancing the lipid solubility of protein molecules *via* hydrophobic ion pairing could increase their intestinal uptake and bioavailability. However, this hypothesis is challenged by the rapid dissociation of hydrophobic ion paired complexes within the GI fluids.

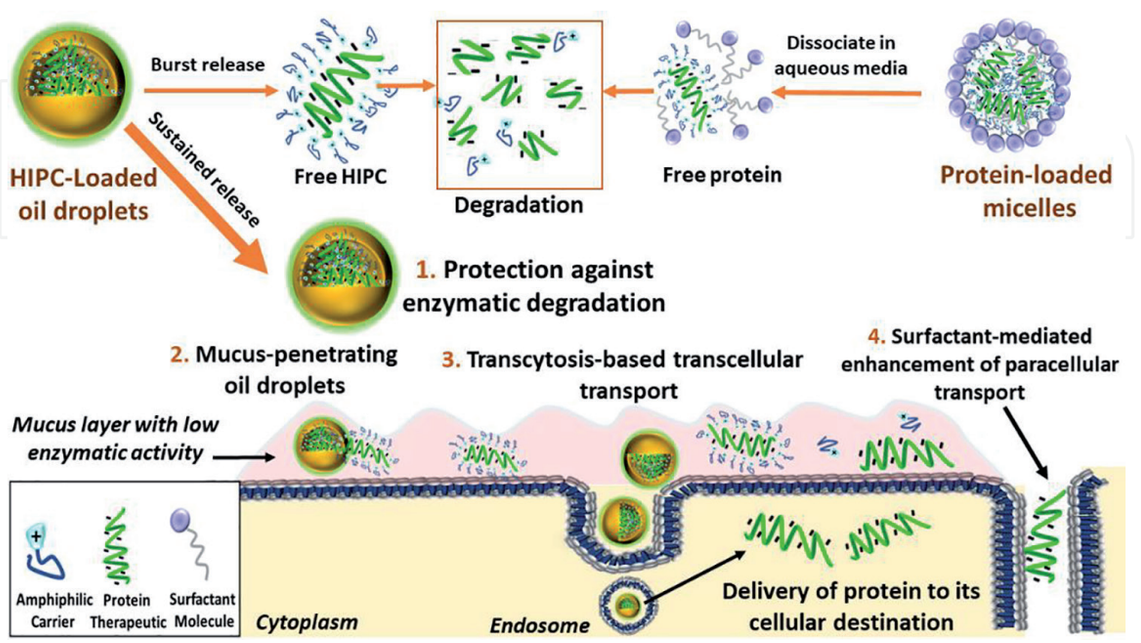

Figure 1.
A schematic representation of some underlying mechanisms for the enhanced oral bioavailability of protein therapeutics by SEDDS (HIPC, hydrophobic ion paired complex). Reprinted with permission from Ref. [33] © Elsevier (2018).

3.3 SEDDS as promising vectors for oral delivery of genetic materials

Oral gene therapy allows the sustained production of therapeutic proteins locally at the disease site as well as for systemic absorption [63]. Unfortunately, the oral delivery of plasmid DNA (pDNA) as well as other nucleic acid products is challenged by their safe and efficient delivery as well as cellular internalization and processing [64]. SEDDS have been investigated as promising non-viral vectors for oral delivery of genetic materials. The superior cellular permeation and stability of pDNA loaded into SEDDS could be mainly attributed to its entrapment within the ultrafine nanoemulsion oil droplets.

3.4 Characterization of SEDDS

3.4.1 Stability of SEDDS preconcentrates

SEDDS preconcentrates should have sufficient stability to avoid drug precipitation as well as creaming or phase separation of the resulting nano- or microemulsions. If some components of SEDDS preconcentrate undergo physical or chemical instability, the resulting emulsion may become unstable [20]. Thus, the stability of SEDDS preconcentrate should be evaluated by subjecting the nano- or microemulsion, resulting from aqueous dilution of the preconcentrate, to a centrifugation study at 5000 rpm for 30 min [65]. Then, SEDDS preconcentrates are subjected to heating–cooling cycle which includes six cycles of storage at 4 and 40°C for 48 h at each temperature followed by freeze–thaw cycle which involves three cycles of storage at −21 and 25°C for 48 h at each temperature [66].

3.4.2 Robustness to dilution

Robustness of the resulting emulsion to dilution guarantees the absence of drug precipitation when SEDDS preconcentrates are subjected to high dilution folds *in vivo* [21]. Thus, SEDDS preconcentrates should be exposed to different dilution folds (e.g., 50-, 100-, and 1000-folds) with different media (e.g., 0.1 N HCl and phosphate buffer, pH 6.8) to mimic *in vivo* conditions [20].

3.4.3 Assessment of self-emulsification efficiency

Self-emulsification efficiency is assessed by determining self-emulsification time and the efficiency of preconcentrate dispersibility when it is exposed to aqueous dilution. The SEDDS preconcentrate is added drop wise to aqueous media with different pH values and composition in a standard USP dissolution apparatus. Self-emulsification time is determined visually as the time required for the preconcentrate to form a homogenous dispersion [21]. The efficiency of preconcentrate dispersibility is also determined visually and is given in grades according to previously reported grading systems [20, 67, 68]. The selection of the appropriate grading system depends on the dilution fold to which the preconcentrate is exposed. This test ensures the ability of SEDDS preconcentrates to disperse quickly in order to form fine emulsions when they are exposed to aqueous media under mild agitation provided by the GI peristaltic movement.

3.4.4 Cloud point measurement

Cloud point could be measured after 100-fold dilution of the preconcentrate with distilled water which is then placed in a water bath with gradual increase

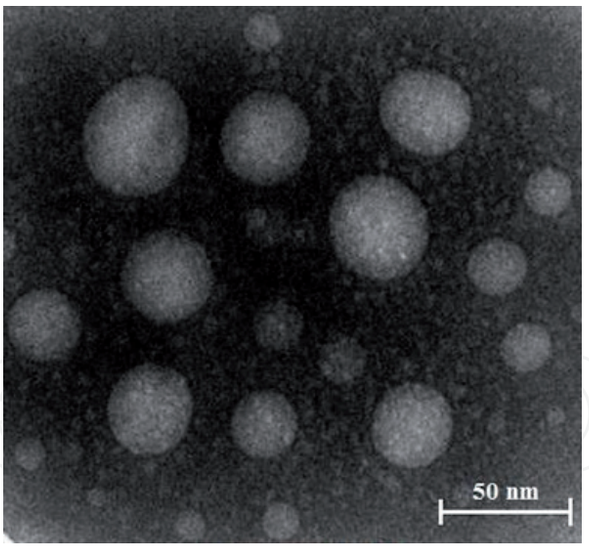

Figure 2.
Transmission electron microscope photograph shows spherical nanoemulsion droplets without any signs of aggregation. Reprinted with permission from Ref. [20]. © Elsevier (2017).

in temperature. Cloud point is determined as the temperature above which the emulsion clarity turns into cloudiness which is attributed to the dehydration of polyethylene oxide moiety of non-ionic surfactants [69]. Cloud point values should be sufficiently higher than 37°C (i.e., normal body temperature) to avoid phase separation in the GI tract [70].

3.4.5 Determination of zeta potential, mean droplet size and polydispersity index

Mean droplet size affects the *in vivo* performance of SEDDS. Small mean droplet size provides large interfacial area for drug absorption and ensures the kinetic stability of the resulting emulsion. Small value of polydispersity index suggests good uniformity of droplet size distribution. High zeta potential values confirm the electrical stability of emulsion droplets and absence of aggregation [66].

3.4.6 Droplet morphology

The morphology of emulsion droplets could be determined by transmission electron microscopy after appropriate dilution of SEDDS preconcentrate (about 1000-fold) using 2% solution of either phosphotungstic acid or uranyl acetate for negative staining. Droplets should possess a spherical shape without any signs of aggregation or drug precipitation as shown in **Figure 2**.

3.4.7 In vitro lipolysis

Drugs incorporated into lipid-based formulations are already present in a dissolved form. Thus, the assessment of the applicability of these formulations should be more properly based on the rate of drug precipitation over time. On the other hand, the drug solubilization capacity of lipid-based formulations is not a function of formulation characteristics alone. Rather, formulation dispersion and digestion result in the formation of colloidal species that account for the intestinal solubilization capacity [71]. Consequently, possible changes to solubilization capacity that could be attributed to digestion of formulation ingredients or interaction with biliary solubilizing agents should be assessed. *In vitro* lipolysis models simulate the GI environment and better predict the *in vivo* behavior of lipid-based formulations

such as SEDDS. They also assess the extent of drug precipitation as a result of digestion of formulation ingredients and changes to solubilization capacity [72].

4. Solid self-emulsifying drug delivery systems

It was reported that ~70% of newly discovered drug molecules and ~ 40% of marketed drugs for oral administration are classified as practically insoluble in water. Therefore, various strategies have been explored to enhance the aqueous solubility and thus oral bioavailability of these drugs. SEDDS have been investigated as an efficient strategy that allows drug administration in pre-solubilized form ready for absorption. Consequently, drugs loaded into SEDDS preconcentrates avoid the dissolution step that frequently limits their absorption. However, the widespread application of liquid SEDDS is challenged by low stability during handling or storage [73] and irreversible drug and/or excipient precipitation [74]. Thus, the majority of marketed liquid SEDDS are filled into soft gelatin (e.g., SandimunneNeoral®, Norvir®, Fortovase®, and Convulex®) or hard gelatin capsules (e.g., Gengraf® and Lipirex®) to be administered as a unit dosage form [75]. However, this approach still possesses the possibility of drug precipitation upon exposure to aqueous media. Additionally, capsule technologies have some limitations such as high production cost and the risk of interaction between the active pharmaceutical ingredient and excipients with the capsule shell. Also, the possibility of drug leakage out of the capsule shell and capsule aging represent further obstacles [76]. Further, the storage temperature is an important consideration since the drug and/or excipients could undergo precipitation at lower temperatures [75]. The tendency of volatile excipients to evaporate into the capsule shell results in drug precipitation and a consequent alteration of drug release [77].

Thus, to address these limitations solid self-emulsifying drug delivery systems (s-SEDDS) were developed by converting the conventional liquid SEDDS into powders which are subsequently filled into capsules or formulated as solid dosage forms such as self-emulsifying tablets, granules, pellets, beads, microspheres, nanoparticles, suppositories and implants [74, 78]. Various solidification techniques for converting liquid SEDDS into s-SEDDS are discussed below.

4.1 Solidification techniques for converting liquid or semisolid SEDDS to s-SEDDS

4.1.1 Adsorption to solid carriers

Adsorption to highly porous and/or high specific area solid carriers is the most intensively explored approach to obtain s-SEDDS [75]. This technique could be effectively used to produce s-SEDDS by simple mixing of solid carriers with the liquid formulation in a blender [74]. The most frequently employed carriers for adsorption of liquid SEDDS formulations are: (i) silicon dioxide such as Aerosil® (fumed silica) and Sylysia® (micronized amorphous silica); (ii) Neusilin® (magnesium aluminometasilicate) which is available in different surface properties and particle size; (iii) Fujicalin® (porous dibasic calcium phosphate anhydrous) and (iv) calcium silicate [75].

Advantages of this solidification technique include:(i) good content uniformity of the produced powders [79]; (ii) high drug loading efficiency (up to 80% *w/w* without affecting flow properties) [80]; (iii) absence of organic solvents [81]; (iv) cost effectiveness because small number of excipients and basic equipment are required for the final formulation and (v) production of free-flowing powders that can be filled into capsule or compressed into other solid dosage form [82].

During the formulation of s-SEDDS by adsorption technique, careful consideration should be given to the possible interactions between the solid carrier and the drug or other excipients in liquid SEDDS which could result in delayed or incomplete release of loaded drug [83]. Additionally, the particle size, specific surface area, tortuosity of pores as well as type and liquid SEDDS: carrier ratio should be considered [75].

4.1.2 Spray drying

Spray drying is also a promising technique for transforming liquid SEDDS to s-SEDDS using different carriers (i.e., hydrophobic or hydrophilic carriers) which preserve the self-emulsifying properties of the formulation. It is a simple and economical technique which involves mixing of lipids, surfactants, drug and solid carriers followed by solubilization and spray drying. The solubilized mixture is atomized into a spray of fine droplets that are introduced into a drying chamber where the volatile phase evaporates forming dry particles under controlled conditions of temperature and airflow [74]. The type of carrier can affect the rate of release and thus the oral bioavailability of loaded drug by affecting the droplet size of the nano or microemulsion formed after reconstitution [84]. Also, careful consideration should be given to the atomizer, the airflow pattern, the temperature and the design of the drying chamber which should be selected according to the powder specifications. Low yield is a disadvantage of solidification by spray drying technique which could be attributed to the removal of non-encapsulated drug with the exhausted air [85].

4.1.3 Extrusion/spheronization

Extrusion/spheronization is the most explored technique for the production of uniformly sized self-emulsifying pellets [75]. Extrusion is a procedure of converting a raw material with plastic properties into a spaghetti-shaped agglomerate having uniform density. Extrusion is followed by spheronization where the extrudate is broken into spherical pellets (spheroids) of uniform size [86]. The produced pellets have good flowability and low friability. Before pellet production, the wet mass is composed of liquid SEDDS, lactose, microcrystalline cellulose (MCC) and water. A disintegrating agent could be added to enhance drug release [87]. MCC acts as adsorbent for the liquid SEDDS to ease pellet formation and avoid problems such as poor flow properties, pellet agglomeration and low hardness. Larger amount of liquid SEDDS can be loaded into the pellets when a greater quantity of MCC on the account of lower amount of lactose is employed in the formulation. The ratio of lactose: MCC and liquid SEDDS: water affects the pellets' disintegration time and surface roughness as well as the extrusion force [88].

4.1.4 Microencapsulation

Co-extrusion technique is a promising strategy for microencapsulation of liquid SEDDS into polymeric matrices. This technique employs a vibrating nozzle device equipped with a concentric nozzle. The formed microcapsules are then hardened by ionotropic gelation. Ionotropic gelation is based on the gel formation ability of polysaccharides (e.g., pectin, alginate, carrageenan, and gellan) in the presence of multivalent ions (e.g., Ca^{+2}) [89]. Alginate and pectin are the most intensively investigated natural ionic polysaccharides for formation of microcapsule shell. However, Ca-alginate microcapsules clog the nozzle during the microencapsulation process. On the other hand, pectin microcapsules lack sufficient hardness. Thus, microcapsules composed of an alginate-pectin matrix could be more acceptable than those composed solely of one polymer. Various hydrophilic filling agents

(e.g., lactose) could be added to the shell formation phase in order to prevent core leakage and microcapsule collapse during the drying process. Advantages of microcapsules include predictable GI transit time and large surface area that allow faster drug dissolution. Additionally, they are composed of biocompatible, non-toxic and biodegradable natural polymers [90].

4.1.5 Wet granulation

Different carriers (e.g., Aerosil® 200) were employed to prepare the self-emulsifying granules where the liquid SEDDS acts as a binder. However, granulation with SEDDS produces a broader size distribution and difficult to control aggregation compared with granulation procedure where water is employed as granulating agent [91].

4.1.6 Melt granulation

In this process, powder agglomeration is attained by the addition of binding agent which melts at relatively low temperature such as Gelucire®, lecithin, partial glycerides or polysorbates [92]. While the liquid SEDDS is adsorbed to neutral carriers such as silica and magnesium aluminometasilicate [93]. Melt granulation is advantageous compared to wet granulation since it is a 'one-step' process in which the addition of granulating liquid and the following drying phase are absent [74].

4.2 Characterization of s-SEDDS

SEDDS are combinations of SEDDS and solid dosage forms. Therefore, the characterization of s-SEDDS is the sum of the corresponding evaluation criteria of both SEDDS and solid dosage forms.

4.2.1 Solid state characterization

4.2.1.1 Differential scanning calorimetry (DSC)

DSC is mainly employed to ensure drug incorporation into the s-SEDDS as well as the absence of drug-solid carrier interaction. It is also used to investigate the physical state (i.e., crystalline or amorphous) of the incorporated drug in the final formulation [94]. Transition from the crystalline to amorphous state is common in SEDDS formulations which lowers the drug melting point and improves its solubility and dissolution rate [95].

4.2.1.2 X-ray diffractometry (XRD)

XRD is employed to investigate the physical state of the incorporated drug because it affects both *in vitro* and *in vivo* performance.

4.2.1.3 Scanning electron microscopy (SEM)

SEM is employed to elucidate the structural and morphological features of s-SEDDS and the raw materials as well as to confirm the physical state of loaded drug [96].

4.2.1.4 Fourier-transform infrared spectroscopy (FT-IR)

FT-IR is usually employed to investigate any potential interaction between the incorporated drug and the solid carrier or other formulation excipients [76].

4.2.2 Determination of micromeritic properties

The flow properties of powders are crucial aspect of large-scale production of solid dosage forms because it affects feeding consistency, reproducibility of die filling and dose uniformity. Powder flowability is affected by various physical, mechanical and environmental factors. Thus, various parameters such as angle of repose, bulk density, Carr's index and Hausner's ratio should be assessed to determine s-SEDDS flowability to overcome the subjective nature of individual tests. The angle of repose is a measure of internal cohesiveness of particles. Powders having angles of repose <30° are considered as free flowing powders; while, powders with angles of repose >40° are regarded to have extremely poor flowability. On the other hand, powders with angles of repose up to 35° are regarded passable; while, those between 35 and 40° indicate poor powder flow which requires the addition of a glidant [97]. Powders having Carr's index up to 21% are considered to have acceptable flow. Hausner's ratios <1.25 are usually corresponded to free-flowing powders with minimum interparticle frictions. On the other hand, Hausner's ratios between 1.25 and 1.5 indicate moderate flow which could be acceptable [98].

4.2.3 Droplet size of reconstituted s-SEDDS

The droplet size of reconstituted s-SEDDS should be similar to that of liquid SEDDS to ensure that the self-emulsification performance of liquid SEDDS is preserved.

5. Conclusion

SEDDS are promising nanocarriers for overcoming various obstacles encountered in the oral delivery of drugs and bioactive agents. The inhibition of P-gp activity by SEDDS relies mainly on the employment of ingredients (i.e., oils and surfactants) with established P-gp inhibition activity in their formulation. Thus, selection of excipients with established P-gp inhibition activity is the first step in the formulation of SEDDS for overcoming P-gp-mediated efflux of substrate drugs and reversing MDR in tumor cells. The effective concentration range for inhibiting P-gp activity should be considered while selecting the formulation ratios. P-gp inhibition activity of SEDDS can be further enhanced by loading other pharmaceutical excipient with established P-gp inhibition activity or traditional P-gp inhibitor. SEDDS are also considered promising systems for the oral delivery of protein therapeutics and genetic materials; however, this role is still in its infancy. Entrapment of these macromolecules within the nanosized emulsion droplets guarantees effective delivery. The bioactive effects of SEDDS ingredients could further enhance the oral bioavailability of protein therapeutics. Liquid SEDDS could be transformed into s-SEDDS to further enhance the formulation stability, allow cost effective large-scale production as well as to enhance the patient compliance.

Conflict of interest

None.

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Author details

Khaled AboulFotouh, Ayat A. Allam and Mahmoud El-Badry*
Department of Pharmaceutics, Faculty of Pharmacy, Assiut University, Assiut, Egypt

*Address all correspondence to: elbadry@aun.edu.eg

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