International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 14, Issue 3, 2022

Review Article

A SYSTEMATIC REVIEW ON SUPERSATURABLE SELF-NANO EMULSIFYING DRUG DELIVERY SYSTEM: A POTENTIAL STRATEGY FOR DRUGS WITH POOR ORAL BIOAVAILABILITY

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Received: 19 Jan 2022, Revised and Accepted: 31 Mar 2022

ABSTRACT

The most fundamental important extensive constitutive of drug molecules to be available for systemic absorption is aqueous solubility; subsequently, that is the nature of GIT fluid. When the drug molecules become solubilized, it has to reach the systemic circulation via the biological membrane. The solubility problem of many effective pharmaceutical molecules is still one of the major challenges in the formulation of this molecule. Drug molecules that belong to class II have a problem in bioavailability mainly due to low aqueous solubility and the rate-limiting step is the dissolution process and so electing of suitable drug delivery and proper additives are decisive to overcome this major obstruction and promote the fraction that will reach the systemic circulation. Among the different lipid-based systems, the su-SNEDDSs have gained attention because the inclusion of precipitation inhibitors within su-SNEDDSs helps maintain drug supersaturation after dispersion and digestion in the gastrointestinal tract. This enhances the bioavailability of drugs and minimizes the variability of exposure. Nowadays, supersaturable self-nano emulsifying and nano lipid-based drug delivery systems have constrained a substantial concern from pharmaceutical scientists for managing the oral delivery of poorly water-soluble compounds. By following oral administration, self-nano emulsifying drug delivery systems show complex aqueous dispersion and digestion in the GIT and enduring intestinal lymphatic transport, exorbitant pre-absorptive metabolism by gut membrane-bound cytochrome enzymes and preventing P-gp mediated drug efflux.

Mostly these processes result in drug supersaturation, which leads to increased absorption or the high drug concentrations may cause precipitation with capricious and variable oral bioavailability. This procession review briefly summarized drug supersaturation obtained from self-nano emulsifying and other lipid-based formulations and this review also delineate the effects of numerous physiological factors and the probable interactions between PIs and lipid, lipase or lipid digested products on the *in vivo* performance of su-SNEDDS and focuses on reviewing the application of su-SNEDDS in enhancing the solubility and bioavailability of anti-cancer drugs in cancer therapy.

Keywords: Su-SNEDDS, Supersaturation, Bioavailability, Precipitation inhibitors, Cancer, Poorly aqueous solubility, Nanotechnology

DOI: https://dx.doi.org/10.22159/ijap.2022v14i3.44178. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

About two-thirds of new drugs in drug discovery reveal low aqueous solubility in water due to which it becomes turn into arduous for formulations to develop oral solid dosage forms with a pharmaceutically acceptable range of therapeutic activity. Drugs of Class II or IV, as per the Biopharmaceutical classification system exhibit poor aqueous solubility. The oral delivery of these drugs is affected by low bioavailability, erratic absorption, inter and intrasubject variability, and lack of dose solubility. Another important factor that affects oral bioavailability is poor gastrointestinal permeability. Several other techniques, including liposomes, cyclodextrin, SLN, complexation, micronization, microemulsions, solid dispersions, and lipid-based formulations, have been developed to overcome these concerns. Hence to enhance their solubility and to increase their oral bioavailability, lipid-based formulations have emerged as a boon. Many approaches were developed to overcome this issue with a variable degree of success, from these approaches, the self-emulsifying drug delivery system (SEDDS) is extensively tried.

Self-emulsifying drug delivery systems (SEDDSs) are a constitutive strategy to enhance the bioavailability of formulations of poorly water-soluble compounds. However, these formulations have some limitations, comprising of vivo drug precipitation, poor *in vitro in vivo* correlation due to an inadequacy of predictive *in vitro* tests, issues in the liquid formulation, and the physicochemical instability of the drug. To overcome these circumspections, the possible form of such systems is restricted, and the supersaturable SEDDSs (su-SEDDSs) have gained attention based on the certainty that they consist of the inclusion of precipitation inhibitors (PIs) within SEDDSs helps maintain drug supersaturation after dispersion and digestion in the gastrointestinal tract. This improves the therapeutic efficacy and bioavailability of drugs and reduced toxicity can be achieved by targeted drug delivery.

Supersaturable formulations promote a supersaturated drug concentration and through co-formulation with precipitation inhibitors and this type of synergic effect can be achieved through Pls and also maintain drugs in a supersaturated state when exposed to the aqueous environment of the gastrointestinal tract.

SEDS

Self-emulsifying drug delivery system (SEDS) is an isotropic mixture of oils, surfactants, cosurfactants, and at times cosolvents, which emulsify extemporaneously to produce oil-in-water or water-in-oil emulsion when introduced into the gastrointestinal tract [1]. Based on the droplet size after emulsification, they are classified into two broad classes, namely self-emulsifying drug delivery systems (SEDDS) with a droplet size range varying between 100-300 nm and self-micro emulsifying drug delivery systems (SMEDDS) with a droplet size range<50 nm [2]. As a result of the lower globule size, the micro/nano emulsified drug can be taken up efficiently through lymphatic pathways, where it bypasses the hepatic first-pass effect [3]. Larger lipid droplet which represents SMEDDS or microemulsions, is converted into smaller micelles on encountering bile salts and lipases and on absorption through intestinal villi help enhance the absorption of the drug [4].

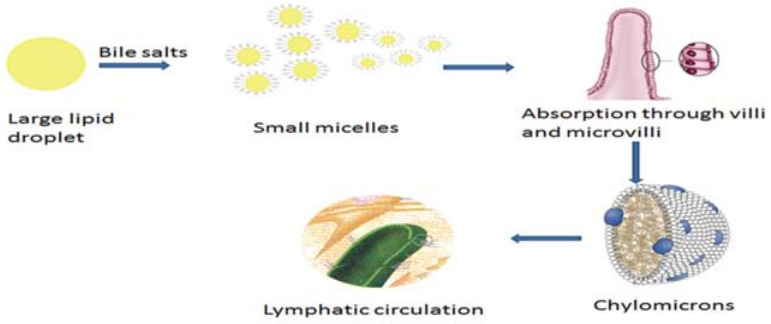

Fig. 1: Absorption mechanism of lipid-based systems (Reprinted from [25] with permission (AJP 2019)

Furthermore, the miniscule globule size, micro-emulsified drugs are easily absorbed through lymphatic pathways, bypassing the hepatic first pass effect. Predominantly, the drug absorption across the intestinal epithelium enhances substantially for highly permeable (BCS) class II and class IV drug molecules when formulated as SEDDSs [5]. These conventional solubilized SEDDSs have several advantages in absorption, there are certain limitations [6], like the drug precipitation *in vivo*, and another limitation of a conventional solubilized SEDDS is toxicity.

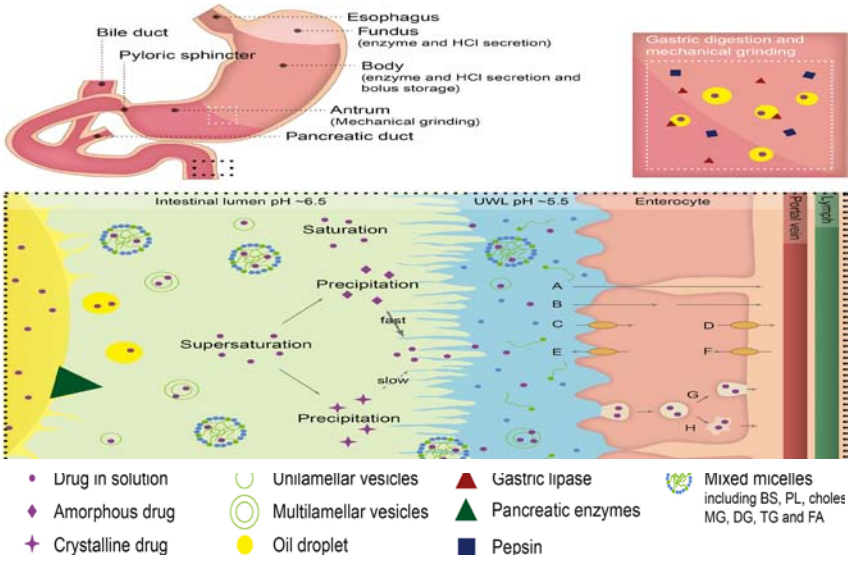

Fig. 2: Schematic presentation of lipid digestion, drug solubilization, and absorption processes occurring in the stomach and small intestine. Reprinted from [7] with permission (Elsevier 2019). For this system, other limitations include a high surfactant concentration is usually required to sufficiently stabilize the high surface area of the lipid–water interface and during storage that the drug remains in a dissolved state and also upon oral administration. Subsequently, solubilized SEDDSs essentially contain high concentrations of surfactants [7]. These high doses of surfactants can lead to gastrointestinal side effects and the conventional dissolution techniques cannot be applied for self-Nano emulsifying drug delivery system as they are dependent on digestion former to dissolution, the *in vitro-in vivo* correlations of SNEDDS must be studied further [8, 9]

Supersaturated self-emulsifying drug delivery systems (Su-SEDDSs)

To conquer drawbacks of solubilised SEDDS, a new class of supersaturable formulation has been designed and developed as a thermodynamically stable self-emulsifying drug delivery system to resolve above limitations.

These su-SEDDS formulations contain a reduced amount of surfactant and a hydrophilic Polymeric Precipitation Inhibitor (PPI) for generating and maintaining a supersaturated state *in vivo* by preventing or minimizing the precipitation of the drug [10]. Many research groups have demonstrated that supersaturable formulations are a promising alternative to improve the oral bioavailability [11].

Theoretically, drugs at high concentrations have an increased driving force for flux across the GI membrane, and enhanced absorption could be achieved with a sufficient period [12]. The main designing of supersaturation is to increase the thermodynamic activity of the drug beyond its solubility limit and, hence, to create increase free drug concentrations with a stronger driving force for move into and across biological barriers, thus resulting in a more effect on the uptake flux.

Oils

The oil is used in SNEDDS formulation for solubilizing the lipophilic drug and ease self-emulsification to increase the amount of drug passing through the intestinal lymphatic system, thus, enhancing absorption. The long and medium-chain triglycerides with varying saturations are employe [13-16]. Hydrolysed vegetable oils are used due to the formation of superior emulsification systems; these systems are accepted for oral administration and semisynthetic medium-chain derivatives, such as, medium-chain triglycerides, e. g., caprylic/capric triglyceride, Miglyol®, and Captex® have also been highly developed. The edible oils are not chosen for SNEDDS formulation due to their ineptitude in solubilizing larger drug concentrations.

Table 1: Commonly employed oil components in the preparation for oral delivery

General class examples	Examples commercial name	Commercial name	References
Fatty acid esters	Ethyl oleate Crodamol EO	Crodamol EO	[196]
Fixed oils	Castor oil, Soyabean oil	-	[196]
Vitamins	Vitamins E	Aqua Gem-E	[197]
Medium chain triglycerides	Tryglycerides of capric/caprylic acids	Miglyol 812, Labrafac CC, Crodamol GTCC	[196]
	Triacetin	Captex 500	[196]
Medium-chain mono-diglycerides	Mono-and diglycerides of Imwitor 742, Capmul MCM diglycerides	Imwitor 742, Capmul MCM	[198]
Long chain monoglycerides	Glyceryl momooleate	Peceol, Capmul GMO	[198]
Fatty acids	Oleic acid Crossential O94	Crossential 094	[200]
	Caprylic acid	-	
Propylene glycol fatty acid esters	Propylene glycol monocaprylate	Capryol 90, Capmul PG-8	[198]
	Propylene glycol dicaprylate/caprate	Miglyol 840, Captex 200	

Surfactants

The non-ionic surfactants are orally acceptable that possess a higher hydrophilic-lipophilic balance. Mostly employed emulsifiers include ethoxylated polyglycolyzed glycerides and polyoxyethylene oleate. Natural emulsifiers are considered safer than synthetic versions, but surfactants possess incomplete self-emulsifying ability. Non-ionic surfactants have lesser toxicity compared to ionic surfactants and direct to increase permeability through the intestinal lumen, and these can be used alone or in combination [17-20].

Table 2: Generally employed surfactants in preparation for oral delivery

General class	Examples	Commercial name
Polyoxyethylene hydrogenated castor oil	Polyoxyethylene 40 hydrogenated castor oil	Cremophor RH40, HCO-40
	Polyoxyethylene 60 hydrogenated castor oil	
Polyoxyethylene stearate	Polyethylene glycol-660-12-hydroxysterate	Solutol HS 15
Polysorbates	Polyoxyethylene-20-sorbitan monooleate Tween 80	Tween 80
	Polyoxyethylene-20-sorbitan monolaurate	Tween 20
Sorbitan esters	Sorbitan monooleate	Span 80
	Sorbitan monolaurate	Span 20
PEO-PPO-block copolymers	Poloxamer 188	Pluronic F68
	Poloxamer 407	Pluronic F127
Polyglycolyzed glycerides	Oleoyl macrogol glycerides	Labrafil 1944 CS
	Caprylocaproyl macrogol glycerides	Labrasol
	Lauroyl macrogol glycerides	Gelucire 44/14
Polyoxyethylene vitamin E	Tocopheryl PEG 1000 succinate	Vitamin E TPGS
Polyoxyethylene castor oil	Polyoxyethylene 35 castor oil	Cremophor EL
Polyoxyethylene stearate	Polyethylene glycol-660-12-hydroxysterate	Solutol HS 15

Co-surfactant

The addition of co-surfactant along with surfactants lower the interfacial tension to–ve value, where it expands to form fine droplets that are consequently adsorbed larger quantities of surfactant and surfactant/co-surfactant till the interfacial tension turns+ve. This process is called "spontaneous emulsification" [21].

Active drug candidate

Preferentially those in BCS classes II and IV. The drug candidate should be a poorly water-soluble drug with an intermediate partition coefficient (log P between 2-4) [22-28].

PIs

Polymeric precipitation inhibitors employed in supersaturable SMEDDS formulation are mainly water-soluble cellulosic polymers like HPMC, PVP, Methyl cellulose, HPMC phthalate, hydroxypropyl methylcellulose acetate succinate (HPMCAS), sodium CMC which can sustain the supersaturated state by preventing the precipitation of drug [29]. The precipitation inhibiting capacity of the three hydrophilic polymers has been found to be in the order PVP K174PEG 40004HPMC. PVP K17 (0.5%) has been found to efficiently retard precipitation [30-35]. PIs can inhibit crystal nucleation and/or growth through their interactions with the drug molecules. Conversely, the drug precipitation can also be prevented thermodynamically by increasing drug solubility. An increased drug solubility by various solubilizing agents such as surfactants, co-solvents, and CDs can reduce the degree of supersaturation, decreasing the nucleation rate. A phase diagram study is preferentially required to obtain an optimal formulation design. Optimized formulations should be selected (i) to achieve maximal drug loading; (ii) to achieve a minimal self-emulsification time and small uniform droplets in the GI fluid for maximal absorption; and (iii) to prevent/minimize drug degradation/metabolism under *in vivo* physiological conditions. Then, for su-SEDDSs, a PI is added to the pre-concentrate formulation. Finally, the liquid state su-SEDDS should be converted to a suitable dosage form [36]. Some of the Pls are given in table 3. Other mechanisms of precipitation include

i). Hydrogen bonding between drug and polymer

Hydrogen bonding interaction between drug and polymer could inhibit the growth of crystals as well as the nucleation process. It has been seen that if the drug has hydrogen bond donor sites (hydroxyl, amide group) is always interacted with acceptor site such as PVP, which inhibits the precipitation through the formation of hydrogen bond interaction between polymer-drug [37-40].

ii). Hydrophobicity and rigidity

Hydrophobicity and rigidity of polymer are affecting the precipitation process. Generally, that moderate hydrophobic polymer are more effective than highly hydrophobic polymer or highly hydrophilic polymer due to weak adsorption of polymer to the drug crystal surface [41].

iii). Molecular weight and steric hinderance

Polymer adsorption capacity depends on the molecular weight of polymer. It has been investigated that high molecular weight polymer are the efficient choice for supersaturated solution [42, 43].

It was shown that PVP 2000 seen less crystal inhibiting capacity than PVP due to low molecular weight and the PVPK90 has a better inhibiting effect than PVP K12, PVPK29 and PVPK32 [44].

Table 3: Various precipitation inhibitors and their performance with active drug

Drug/Active compound	Precipitation inhibitor	Intent	Reference
Piroxicam	HPMC	Investigation of rate of *in vitro* penetration across silicon membrane and full thickness human skin.	[187]
Ricobendazole	HPβCD	Sheep PK study showed 2.2-fold increase in Cmax and 1.6-fold increase in AUC	[186]
Felodipine	HPMC	Evaluating the impact of HPMC on the crystal growth and nucleation kinetic of supersaturated solution.	[197]
Paclitaxel	CD, HPβCD	Higher than 80% oral bioavailability achieved	[195]
Saquinavir	HPβCD	Saquinavir precipitation avoided in seminal fluid simulant with 12% PEG 1000+2.5% HPβCD	[103]
Griseofulvin	Polooxamer and HPMC	Design and investigation of exvivo intestinal permeability study of griseofulvin	[199]
Indirubin	PVP K17	Rat PK study showed1.3 times higher bioavailability	[42]
Carbamazepine	PVP	Dog PK study showed 5-fold increase in bioavailability compared with the commercial tablet	[126]
Econazole nitrate	HPMC	Improvement of bioavailability by designing ocular supersaturated SNEDDS for improving bioavailability.	[58]
Fenofibrate	Soluplus	Improvement of bioavailability and investigation of precipitation assays of supersaturated formulation.	[199]
Butyl paraben	HPMCAS	At least 0.6 mg/ml of butyl paraben was maintained in the supersaturated condition for 72 h	[127]
PNU-91325	HPMC	A 5-fold higher bioavailability was observed from an S-cosolvent formulation containing PEG+20 mg/g HPMC compared with a neat PEG 400 formulation	[164]
Silybin	HPMC	Enhancement of oral bioavailability of silybin by ss-sedds.	[15]
Cyclosporin A	PVP	For improvement of dissolution rate of cyclosporin A by using PVP as precipitation inhibitor.	[194]
Tacrolimus	HPMC	Dog PK study showed a 10-fold increase in Cmax and AUC compared with crystalline powder	[125]
Paclitaxel	HPMC	Rat PK study showed 10-fold higher maximum concentration and 5-fold higher oral bioavailability.	[163]
Danazol	PVP, HPMC, HPMCAS	Characterization of phase behavior aswell as the degree of supersaturation	[192]
AMG 009	HPMC	17.5-fold increase in dissolution	[132]
Pazopanib	HPMC	Investigation of the phase behaviour of supersaturated solution from low PH followed by higher PH by phase diagram.	[198]

Cyclodextrin complexation

Cyclodextrin have the ability to form inclusion complexes with a variety of hydrophobic drug to increase solubility. The two well-known cyclodextrins which are used to improve the bioavailability of poorly soluble drug are 2-hydroxypropyl-β-cyclodextrin (HPβCD) and sulphobutylether-β-cyclodextrin [45].

Principles of drug precipitation for development su-SEDDSs

Supersaturation is a state in which drugs present above their saturation solubility in solution and are thermodynamically unstable [46]. The degree of supersaturation can be expressed with the relative ratio of the actual concentration of drug in solution to the saturated solubility of the drug as the supersaturation ratio S:

$$S = \frac{C}{C_{eq}} \quad \ldots\ldots (1)$$

Where C_{eq} represents the saturation solubility and C is the experimentally measured actual drug concentration. The relative supersaturation index also can be used to express supersaturation and is defined as:

$$\sigma = S - 1 = (C - C_{eq}/C_{eq} \quad \ldots\ldots (2)$$

Based on the obtained S or a, the state of the drug solution is classified as follows:

1. S<1 (σ<0): unsaturated or subsaturated;

2. S = 1 (σ = 0): saturated;

3. S>1 (σ>0): supersaturated.

Compared with a stable, saturated solution (μ_{eq}), a supersaturated solution is characterized by an increased chemical potential (μ) or activity (a) of the drug in the solution. The thermodynamic driving force for drug precipitation can be formed by the difference in chemical potential (Δμ):

$$\Delta\mu = \mu - \mu_{eq} \quad \ldots\ldots (3)$$

From the definition of chemical potential, it follows that:

$$\Delta\mu = RT.\,In\left(\frac{a}{a_{eq}}\right) \quad \ldots\ldots (4)$$

where a and aeq refer to the activity of the drug in a supersaturated and saturated state, respectively, Rmis the universal gas constant, and T is the temperature of the solution system. Equation (4) can be transformed into Equation (5), assuming no difference between the activity coefficient of the drug in the supersaturated and saturated state:

$$\Delta\mu = RT.\,In\left(\frac{C}{C_{eq}}\right) = RT.\,In(S) \quad \ldots\ldots (5)$$

Where C is the drug concentration in the supersaturated solution, C_{eq} is the equilibrium solubility of the drug in the saturated solution, and S is the supersaturation ratio, as defined in Equation (1). The drug solution is thermodynamically unstable in a supersaturated system; hence, it tends to return to a stable state through drug precipitation.

Compatibility studies

Various analytical methods have been used for characterizing polymer-drug interactions and crystallization process. The results can shed light on potential mechanisms of the inhibition process. Such methods include X-ray diffraction, differential scanning calorimetry, Raman spectroscopy, Fourier transform infrared spectroscopy, X-ray photoelectron spectroscopy, microfluidic technology, polarized microscopy, scanning electron microscope and atomic force microscopy [47-54].

Enhance in absorption by supersaturation in the GIT

Drug absorption can be assessed by Fick's First law; thus, the drug absorption via passive drug diffusion is driven by the maximum concentration in GIT [55]:

$$J = \frac{dM}{dt} = S.P.C$$

where the flux (J) of a drug through the GI barrier wall, which is defined as dM, the cumulative transport mass during dt, depends on the diffusion area (S), permeability coefficient (P) of the drug, and the drug concentration (C) in the GI lumen (assuming sink conditions). From this equation, it can be estimated that increasing the drug solubility can improve the absorption of a poorly water-soluble drug [56, 57].

Factors affecting drug precipitation

The precipitation of drug from supersaturated solutions is a complex function of both nucleation and crystal growth, which in normally, is affected by various factors.

i). Degree of supersaturation: Increasing the degree of supersaturation of SMEDDS formulation favours drug precipitation by increasing nucleation rate. Supersaturation can occur through [58].

(a) Evaporation of solvent from the solution

(b) Cooling of the solution, if solute has positive heat of solution

(c) Formation of a new solute as a result of chemical reaction

(d) Addition of a substance which has higher solubility in the solvent than the solid to be crystallized and addition of solvent that lowers the solubility of the solute.

ii). Solubility: At constant supersaturation, increasing the solubility of SMEDDS increases the probability of intermolecular collision, which thereby increases nucleation rate [59].

iii). Impurities: Presence of impurities in solution stimulates the nucleation process. The presence of impurities decreases the energy barrier for the formation of nuclei which ultimately lead to crystal formation [60, 61].

iv). Temperature: Binding between drug and polymer is decreased at higher temperatures due to weakening of intermolecular interactions between the molecules and increased solubility of drug [62].

v). Solution viscosity: Low solution viscosity favors drug precipitation [63].

Mechanism to restrain drug precipitation

The key to designing and developing supersaturable formulations is to identify the optimal combination of "spring" and "parachute" [64-68]. Hence, the most common strategy to maintain supersaturation is to use Pls, such as polymers, surfactants, and/or cyclodextrins, which can produce a combination of "spring" and "parachute" functions [69].

A number of probable mechanisms are proposed, which include the following factors.

i). Spring and Parachute mechanism: Supersaturable formulations are thermodynamically stable formulations which could induce a supersaturated concentration in an aqueous environment of the gastrointestinal tract [70, 71]. The most common ways to initiate supersaturation is through salts which will rapidly dissolve amorphous solids, co-solvents and self-emulsifying formulations. All these formulations are referred to as springs and a formulation component which hinders nucleation or crystal growth acts a parachute to stabilize the metastable supersaturated formulations for a sufficient time period for absorption to take place. Parachute slowly settles down concentration to the saturation solubility given in fig. 3. The generation of a supersaturated state and subsequent inhibition of precipitation have been referred to as a "spring and parachute" approach [72, 73].

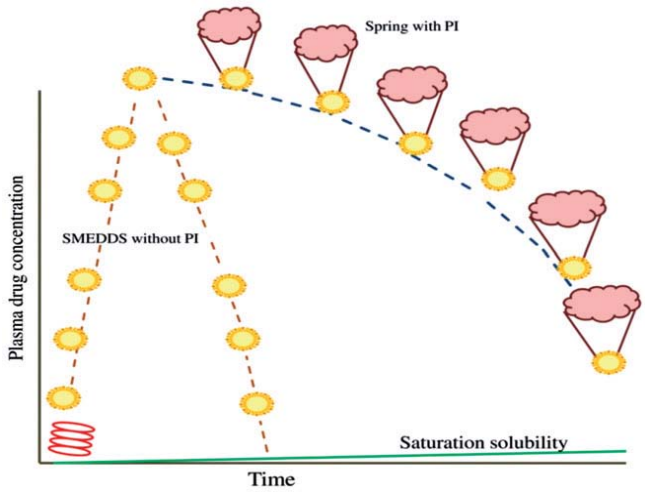

Fig. 3: Spring with parachute mechanism. Reprinted from [25] with permission (Elsevier 2015)

ii). Reticulate formation: Creation of a widely spaced cellulosic polymer network has been proposed to generate a supersaturated state of HPMC with supersaturable SMEDDS formulation.

iii). Hydrogen bonding: HPMC or the hydrophilic polymers can thus form both intramolecular and intermolecular hydrogen bonds with drug, which is likely to retard drug precipitation [74].

Kinetics drug supersaturation

The high drug solubilization of lipid-based formulations is a supersaturation effect; however, there is also a further increase in the solubility limit in the presence of lipids [75]. Fast dispersion occurs in parallel to rapid initial drug release for self-emulsifying systems. This initial increase in concentration beyond the thermodynamic solubility limit has been termed "spring", whereas a "parachute" is the ability to sustain drug supersaturation, as given in fig. 4. The latter concept of supersaturation is often understood as a supersaturation ratio S, as given in below equation:

$$S = \frac{C}{C^*}$$

Where c is the (molar or mass) concentration of supersaturated drug and c* denotes the equilibrium solubility.

Pharmaceutical characterization and evaluation of Su-seddss

The final su-SEDDSs should be characterized for various parameters, including

Droplet size and polydispersity index

The droplet size (z-ave) and polydispersity index (PI value) can be determined by using a photon correlation spectroscopy

technique and Dynamic light-scattering is the most widely used for routine evaluation of emulsion particle size and also small angle X-ray and coulter counter can be used for the droplet size analysis.

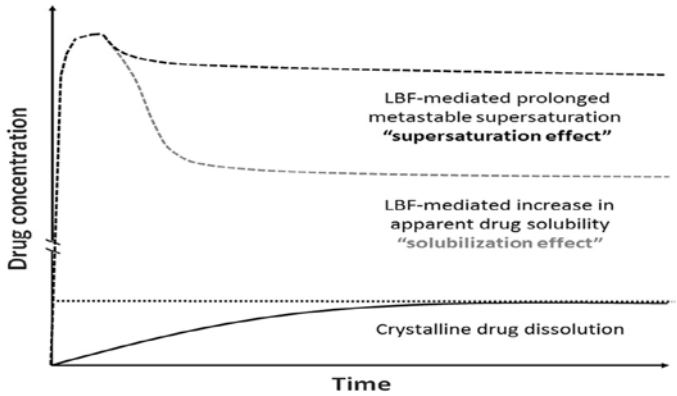

Fig. 4: Idealized concentration profiles of how lipid-based formulations (LBFs) can solubilize a poorly water-soluble drug in the gastrointestinal tract. Reprinted from (62) with permission

Conductivity and viscosity measurements

Conductivity measurements determine the point of aqueous phase addition at which the system changes from having an oil-continuous to a water-continuous phase. They can be applied to monitor the percolation and phase-inversion of emulsion [76]. The viscosity of liquid SNEDDS is generally known by a viscometer, such as, Brookfield cone and plate viscometer.

Self-emulsification properties

The free energy of emulsion formation is a direct function of the energy required to create a new surface between the two phases [77-79]. This self-emulsification process is defined by the equation below:

$$\Delta G = \sum N.\pi.r^2\sigma$$

Where ΔG represents the free energy associated with the process, N is the number of droplets of radius r, and σ is the interfacial energy [80].

Zeta potential

The particle charge of formed nanoemulsions can be determined according to the Smoluchowski theory. Zeta potential indicates the stability of the colloidal dispersion. The formulation will remain stable if it has a high zeta potential, especially when the zeta potential value is more than±30 mV [81].

Morphology

The morphology of the nanoemulsion droplets can be determined by transmission electron microscopy (TEM) and scanning electron microscopy (SEM) [82-85].

Phase separation method

The general method of knowing the stability of SEDDSs is the phase separation method.

Samples diluted with distilled water are centrifuged at a specified rpm for a specified amount of time and their phase separation is investigated. The determination of the cloud point is a crucial tool in the case of SEDDSs containing non-ionic surfactants. At the cloud point, irreversible phase separation occurs owing to an increase in temperature. The cloudiness of the preparation negatively influences the absorption of the incorporated drug because it indicates the dehydration of the SEDDS ingredients. Hence, the cloud point of self-emulsifying systems must be above 37 °C to avoid phase separation in the gastrointestinal tract [86].

Effectiveness of drug loading

The drug loading efficiency is tested and used to determine the fraction of drug-loaded into the solvents. By increasing the concentration of the oily phase, it reduces the loading capacity of the drug [87-90].

$$\text{Drug loading Efficiency} = \frac{\text{Initial Drug Load} - \text{Amount of Drug in Filtrate}}{\text{Initial Drug Load}} \text{x100}$$

Self-nanoemulsification time

The efficiency of self-nano emulsification is assessed using a dissolution apparatus. In this method, 1 ml of the SNEDDS is dissolved in 250 ml of water at 37±0.5 °C. Gentle agitation is applied by paddle rotating at 50 rpm. SNEDDS are assessed visually according to the rate of emulsification and the final appearance of the emulsion. The time taken for the emulsification is noted and particle size is determined by photon electron microscope.

Refractive index

The RI of the system is measured using a refract meter by placing a drop of the solution on a slide and comparing with water, which has an RI of 1.333. If the RI of the system is similar to the RI of water, the formulation has a transparent nature.

Spectroscopic evaluation

For the qualitative and quantitative analysis of lipid-based formulations, spectroscopic techniques can be used as non-destructive methods [91]. Especially, low-frequency dielectric spectroscopy (LFDS) is based on the measurement of conductivity caused by the polarization of a material that occurs after the application of an electrical field. To analyze the intermolecular interactions and drug-excipient compatibilities, considering the structure and dynamics of microemulsions, Fourier-transform infrared spectroscopy, Raman spectroscopy, and nuclear magnetic resonance are the most widely used [92-94].

Small-angle X-ray scattering

Small-angle X-ray scattering (SAXS) has been used for the determination of the microscale or nanoscale structure of particle systems, including the shape and size of macromolecules, characteristic distances of partially ordered materials, pore sizes, and other related data [95].

Biorelevant supersaturation testing

Many research scientists, promising progress has been made in the development of a biorelevant *in vitro* digestion model with good IVIVC for predicting the effects of various GI factors on the performance of supersaturable drug delivery systems, including *in vivo* supersaturation, drug precipitation, and absorption. More recently, improved computational models of the gastrointestinal environment using molecular dynamics showed a great potential to assist the complex process of drug formulation [96, 97].

Percentage transmittance

The percentage transmittance of the system is determined following the dilution of the formulation at 638 nm wavelength by a UV-

spectrophotometer and using the water as blank. If the percentage transmittance value is closer to 100%, the formulation would indicate a clear and transparent nature.

***In vitro* dissolution study**

The *in vitro* dissolution profile of the SNEDDS should be evaluated using a dissolution apparatus Type II in various dissolution media associated with the purposed route of administration, such as, pH 1.2 and pH 6.8 for oral application. The dissolved drug in the dissolution media would be collected during a set period of time and analysed by an appropriate analytical method. Cumulative amounts of drug dissolved against the times of the preparation would be plotted compared with the pure drug.

***In vitro* digestion model**

There has been a development of a range of *in vitro* models simulating the digestion processes occurring in the GIT to evaluate su-SEDDSs. Many reviews have been reported, including detailed explanations [98].

Thermodynamic stability

To overcome the problem of metastable formulation, a thermodynamic stability test would be performed. The liquid Su-SNEDDS would be centrifuged at 3,500 rpm for 30 min. The formulation that does not show any phase separation would be subjected to the heating-cooling cycle. Six cycles between 4 °C and 45 °C for 48 h would be conducted. The formulation that is still stable would then be subjected to the freeze-thaw stress test by achieving three cycles between-21 °C and 25 °C for 48 h. The formulation that endures the thermodynamic stability test would be selected as the stable formulation for further studies.

Stability assessment

The stability study of nanomedicines including the Su-SNEDDS should be performed following the guidelines of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). For the non-targeted nanomedicines, which are free from the regulations for biotechnological products, should follow the procedures of the ICH Q1A(R2) and Q1C guidelines. Meanwhile, the targeted nanomedicines, which are mostly incorporated with biotechnological products, should follow the procedures of the ICH Q5C guideline. Su-SNEDDS should also be evaluated under the storage conditions for their thermal stability and sensitivity to moisture. In general, the recommended long-term and accelerated storage conditions by the ICH guidelines are 25 °C±2 °C/60% RH±5% RH and 40 °C±2 °C/75% RH±5%RH, respectively. Appropriately, an intermediate storage condition (30 °C±2 °C/65% RH±5%RH) is recommended. In addition, if any drug products are intended for storage in a refrigerator, long-term and accelerated storage conditions are recommended at 5 °C±3 °C and 25 °C±2 °C/60% RH±5%RH, respectively [99].

HTP lipolysis model

To evaluate drug precipitation of a large pool of su-SEDDS formulations and select optimum PI, *in vitro* HTP lipolysis model has been required and developed. Presently, it was reported that the HTP lipolysis model become a useful tool to predicts drug dissolution and precipitation during the digestion of lipid-based formulations containing poorly water-soluble drugs in the same manner as pH-stat lipolysis models [100].

Digestion–permeation models

It may provide a better indication of various mechanisms critical to the negation of food effects and the enhancement of overall systemic drug exposure and recent research reported *in vitro* digestion-*in vivo* permeation model, which is called in situ perfusion [101, 102].

***In vitro* evaluation of solid su-SEDDSs**

Whether the emulsion is formed as originally designed and has the desired properties after solidification should be evaluated [103]. After the re-emulsification evaluation mentioned below, evaluation using the emulsion characterization methods.

Re-emulsification and drug release from solid su-SEDDSs

Solid su-SEDDSs should maintain their self-emulsifying ability and should be able to be forming fine oil-in-water emulsions under the gentle agitation provided by GI motion. The drug is introduced in a dissolved state and has a huge interfacial area for absorption provided by the emulsion droplets, resulting in enhanced bioavailability. As the drug is transferred from solid su-SEDDSs into the dissolution medium and solubilized in the oil/surfactant emulsion droplets, the rate of release is expected to be controlled by the rate of re-emulsification and the completeness of reconstitution.

Stability assessment

The stability study of nanomedicines, including the SNEDDS should be performed following the guidelines of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) For the non-targeted nanomedicines, which are free from the regulations for biotechnological products, these should follow the procedures of the ICH Q1A(R2) and Q1C guidelines and the targeted nanomedicines should follow the procedures of the ICH Q5C guideline [104].

Pharmaceutical excipient for solidification

The proper solid excipients for the solidification of su-SEDDSs should be adapted precisely because of their critical implications for not only the physicochemical properties of the su-SEDDS formulation but also *in vivo* drug absorption from the formulation. The water-insoluble mesoporous silica and Microcrystalline cellulose (MCC), water-soluble polysaccharide, or polymer or protein-based solid carriers are generally used as solidification excipients [105]. Eminently, some of the application cases in su-SEDDS have been reported, given in table 2. Many reviews have broadly discussed the properties of these excipients and in this review, only the summarised information about various solidification process for Su-SEDDS is mentioned in table 4 and an overview of approved anti-cancer nanodrugs are given in table 5.

Table 4: List of drugs that have been formulated into supersaturable self-emulsifying drug delivery system (Su-SEDDS)

Drug (BCS class)	Preconcentrate	PI		Dosage form (Solidification method)	Result/Outcome	Ref.
	Formulation (Drug Conc.)	Substance (Conc.)	PI Addition method			
Resveratrol (BCS II)	Lauroglycol FCC, Transcutol P (100 mg/450 mg)	HPMC-E15LV(5%*w/w*)	Suspending ine pre-concentrate by vortexing (Suspension)	Liquid	-*In vivo* in Wister rats at a dose of 20 mg/Kg, 1.33-fold increase AUC of the su-SEDDS than conventional SEDDS without PI.	[146]
Silybin (BCS II)	Labrafac CC, Cremophor RH40, Labrasol (40 mg/1090 mg)	HPMC-E50LV (5% w/w)	Suspended in preconcentrate by vortexing (Suspension)	Liquid	-*In vivo*in SD rats at a dose of 533 mg/kg, three-fold increased AUC than those of the t conventional SEDDS without HPMC	[147]
Siliymarine (BCS II)	Labrafil M 1944 CS, Kolliphor® RH 40, Transcutol HP (15.6% as milk thristle powder, w/w)	Poloxamer 407 (10%w/w)	Dissolving in pre-concentraate by heating and magnetic stirring (Poloxamer 407: Clear	Liquid	-PI effect: Poloxamer 407>HPβCD, HPMCP, Eudragit L100. -*In vivo* in Rabbits at a dose of 28	[148]

Drug (BCS class)	Preconcentrate	PI		Dosage form (Solidification method)	Result/Outcome	Ref.
	Formulation (Drug Conc.)	**Substance (Conc.)**	**PI Addition method**			
			solution). Suspending in pre-concentrate by milling (Other Pls: Suspension)		mg/kg as silybin, 760% BA of su-SEDDS vs Legalon®, commercial products.	
Tacrolimus (BCS II)	Capmul MCM, Cremophor EL, and Transcutol P (5.9%,w/w)	Soluplus (5.9%, w/w)	Suspended in preconcentrate by vortexing using a magnetic stirrer (Suspension)	Liquid	-PI effect: Soluplus>HPMC, PVP. -Concentration-dependent PI effect -*In vivo* in SD rats at a dose of 5 mg/kg. Similar or higher AUC and Cmax of su-SEDDS containing one-quarter the amount of vehicle compared to conventional SEDDS.	[149]
Valsartan (BCS III)	Capmul MCM, Tween 80, Gelucire 44/14, water (80 mg/190 mg)	Poloxamer 407 (5.3 %,w/w)	Adding in pre-concentrate	Solid su-SEDDS (Kneading and granulation by sieving, HPC and Florite® PS-10)	-Concentration-dependent PI effect -*In vivo* in SD rats at a dose of 10 mg/kg. Approximately 177%-198% AUC versus raw drug and Diovan®, commercial product.	[150]

Table 4 cont

Drug (BCS class)	Preconcentrate	PI		Dosage form (Solidification method)	Result/Outcome	Ref.
	Formulation (Drug conc.)	**Substance (Conc.)**	**PI Addition method**			
Dutasteride (BCS II)	Capryol 90, Cremophor EL, Transcutol HP (100 mg/20.1 g)	HPMC, Solupus(1:1 w/w ratio compared to pre-concentrate)	Mixing with pre-concentrate (2.01 g) anad PI solution (2g in 400 ml EtOH) dispersed with solid carrier, Aerosil 200 (2g)	Solid su-SEDDS(Spray drying)	-*In vivo* in SD rats at a dose of 2 mg/kg, higher oral BA with 6.8 and 5.0-fold for C_{max} and AUC, respectively, compared to the physical mixture.	[118]
Dutasteride (BCS II)	Capryol 90, Cremophor EL, Transcutol HP (Drug: Vehicle=1:67.6,w/v)	Soluplus Vehicle=10:67.6(w/v)	Suspending in preconcentrate by vortexing (Suspension)	Liquid	-*In vivo* in SD rats at a dose of 2 mg/kg, 3.9-fold greater AUC than that of drug suspension.	[198]
Ellagic acid (BCS IV)	Ethyl oleate, Tween 80, polyethylene glycol (4 mg/g)	PVP K30 (0.5%, w/w)	Adding in preconcentrate by vortexing	Liquid	-Concentration-dependent on PI effect. -Good correlation between *in vitro* nucleation inhibition effect of PI and *in vivo* antioxidant ability.	[153]
Fenofibrate (BCS II)	Ethyl oleate, Cremophor RH40, Transcutol HP (15%w/w)	Soluplus: Drug=1:1(w/w)	Physical blending with solid su-SEDDS	Solid su-SEDDS(Solvent evaporation, mesoporous silica)	-*In vivo* in beagle dogs at a dose of 100 mg, 1.4-fold greater AUC than that without Soluplus.	[78]
Fenofibrate (BCS II)	Captex 300, Capmul MCM, Cremophor EL, Transcutol HP (40% or 85% of saturated solubility in formulation)	Lipid soluble: Eudragit RL100(5%,w/w), PPGAE(1%,w/w) Water soluble: HPMC E4M (5%,w/w)	Dissolving in pre-concentrate by vortexing (Lipid soluble: Clear solution, Water-soluble: Suspension)	Liquid	-Polymer specific stabilizing agent -*In vitro*-in situ model using SD rats, potential utility of PPIs in promoting drug absorption via stabilization of supersaturation.	[19]
Ezetimibe (BCS II)	Captex 355, Cremophor RH40, Imwitor 988(90% saturation solubility level of 90.62 mg/ml)	HPMC-E5 (5%, w/w)	Suspending in preconcentrate by Cyclo-mixer (Suspension	Solid su-SEDDS(Adsorption and granulation, MCC and talc))	*In vitro* release improved by 1.18-1.69, and 13.21-fold as compared to solid-SEDDS, commercial product, and the free drug, respectively.	[116]
Curumin (BCS IV)	Capryol 90, Labrafac PG, Cremophor EL, Labrasol (40 mg/940 mg)	Eudragit E PO (5% w/w)	Suspending in pre-concentrate by blending (Suspension)	Liquid filled in hard gelatin capsule	-*In vivo* in rabbits at a dose of 50 mg/kg, 1.22- and 53.14-fold increased absorption as compared to the conventional SEDDS without PI.	[155]

Table 4: Cont

Drug (BCS class)	Preconcentrate	PI		Dosage form (Solidification method)	Result/Outcome	Ref.
	Formulation (Drug Conc.)	**Substance (Conc.)**	**PI Addition method**			
Cyclosporin A (BCS II)	Maisine 35-1, Kolliphor RH 40, ethanol, and propylene glycol (Drug: Vehicle=1:4.5 (w/v))	PVP: Vehicle = 0.3:4.5 (w/v)	Suspending (HPC) or dissolving (Kollidon VA64 and PVP in pre-concentrate by vortexing (Suspension)	Liquid	-PI effet: Without PI=HPC=PVPVA64<PVPK17 -*In vitro* dialysis test, equivalent concentration profile with that of conventional SEDDS prepared with two times more amount of lipid vehicle	[156]
Danazole (BCS II)	Captex 300, Capmul MCM, Cremophor EL, EtOH (40% or 80% of saturated solubility in formulation)	HPMC E4M (5% w/w)	Suspending in pre-concentrate (Suspension)	Liquid filled in hard gelatin capsule	-PI effect: Cellulosec PPI>Mesoporous silic, Eudragits, PVPs. -*In vivo* in beagle dogs, PPI to promote drug exposure at moderate drug loads (40% of saturated solubility in the formulation), but not at higher drug loads (80%saturation).	[157]
Docetaxel (BCS II)	Labrafac, Cremophor RH40, Transcutol P (40 mg/640 mg)	HPMC K100 (2.5%,w/w)	Dispersing in pre-concentrate (ND)	Solid su-SEDDS(Spray drying, Lactose: pre-concentrates=6g: 8g in 100 ml water)	-*In vivo* in SD rate at a dose of 10 mf/kg, AUC increased by nearly 8.77-fold, 1.45-fold more than those of the powder drug than those of the powder drug and the conventional SEDDS without PI.	[158]
Dutasteride (BCS II)	Capryol 90, Cremophor EL, Transcutol HP(0.5 mg/170 kg)	Gelatin (44%,w/w)+Solu plus (14.7%, w/w0	Mixing with pre-concentrate and PI solution (Clear solution)	Solid su-SEDDS(Spray drying, Gelatin)	-PI effect on dissolution anad prolonged supersaturation state: Combination of gelatin with Soluplus>Gelucire 44/14, poloxamer 407, sodium lauryl sulfate, Soluplus, Solutol HS15 or TPGS.	[159]
AMG 517 (BCS II or IV)	Capmul MCM, Tween 80, PEG 400 (12.5 mg/450 mg)	HPMC-E5 (5% w/w)	Suspending in pre-concentrate by vortexing (Suspension)	Liquid filled in hard gelatin capsule	-PI effect: HPMC>PVP -Hydrophobicity dependent PI effect. -*In vivo* in Cynomolgus monkeys at a dose of 12.5 mg: -30% higher C_{max} and AUC, and short T_{max} as compared to an aqueous suspension.	[19]
Carbamazepine (BCS II)	Miglyol 812 N, Tween 80 Cremphor EL-35, PEG 400 (25 mg/830 mg)	PVP-K90 (2%w/w)	Dissolving in pre-concentrate by heating and stirring (Clear solution)	Liquid filled in soft gelatin capsule	-PI effect: PVP>HPMC -*In vivo* Beagle dog at a dose of 200 mg, 6.7 times higher C_{max}, 5.9 times higher AUC as compared to commercial tablet.	[161]
Celecoxib (BCS III)	PEG 400, EtOH, Tween 80, Oleic acid, Tromethamine, water (200 mg/g)	HPMC-E5(3.8%,w/w)+ PVP-12PF(4.7%w/w)	Suspending in pre-concentrate by vortexing (Suspension)	Liquid filled in hard gelatin capsule	-Highly supersaturated state in the aqueous, resultinh in high drug concentration in octanol for biphasic *in vitro* test dissolution method. -Good *in vitro-in vivo* correlations (IVIVC) with human PK as compared to solution and marketed capsule formulation.	[162]
Drug (BCS class)	**Preconcentrate**	**PI**		**Dosage form (Solidification method)**	**Result/Outcome**	**Ref.**
	Formulation (Drug conc.)	**Substance (Conc.)**	**PI Addition method**			
Celecoxib (BCS III)	Caproyl 90, Tween 20, Transculatol HP (180 mg/ml)	Soluplus (4%, w/v)	Adding in pre-concentrate by vortexing (Suspension)	Solid su-SEDDS (Adsorption method, Sylysia 350 fcp)	-Physico-chemical properties (surface area, hydrophobicity) of solid carrier dependent drug dissolution. -*In vivo* in SD rats, 2.34-fold increase in C_{max} and 4.82 fold increase in AUC as compared to drug powder.	[163]
Celecoxib (BCS III)	Caproyl 90, Tween 20, Tetraglycerol (200 mg/ml)	Soluplus (4%, w/v)	Adding in pre-concentrate by vortexing (Suspension)	Liquiid	-*In vivo* in SD rats at a dose of 100 mg/kg, 1.32-fold increase in C_{max} and 1.35-fold increase in AUC and 0.49-fold decrease in T_{max} as compared to conventional SEDDS without PI. -Good correlation between *in vitro*	[164]

Drug (BCS class)	Preconcentrate	PI		Dosage form (Solidification method)	Result/Outcome	Ref.
	Formulation (Drug Conc.)	Substance (Conc.)	PI Addition method			
					dissolution, permeation and *in vivo* PK	
Pacilitaxel (BCS IV)	EtOH, PEG 400, Cremophor EL, Glceryl dioleate (57 mg/g)	HPMC-ESLV (5% w/w)	Suspending in pre-concentrate by hand mixing (Suspension)	Liquid	-*In vivo* in SD rats at a dose of 10 mg/kg, 10-and 20-fold higher C_{max} and 5-and 10-fold higher AUC compared with those of Taxol® formulation and the conventional SEDDS, respectively.	
PNU-91325 (BCS II or IV)	Cremophor EL, PEG 400, Dimethylacetamide, Pluronic L44, HPMC, Glycerol monooleate, Glycerol dioleate, water (4%, w/w)	HPMC-E50LV (20%w/w)	Suspending in pre-concentrate by vortexing (Suspension)	Liquid filled hard gelatin capsule	-*In vivo* in beagle dogs at a dose of 10 mg/kg. Oral BA of-76% compared to that of a PEG 400 (-12%) or tween(-68%) formulations.	[166]
Indirubin (BCS II or IV)	Maisine 35-1, Cremophor EL, Transcutol P	PVP-K17(0.5%,w/w)	Dispersing in pre-concentrate by vortexing	Liquid	-PI effect: PVP-K17>PEG 4000 and HPMC -*In vivo* in SD rats at a dose of 2.58 mg/kg, improved oral absorption and relative BA (129.5%) compared with conventional SEDDS, respectively.	[102]
Glipizide (BCS II)	Captex 355: SolutolHS15:Imwitor 988 (4%, w/v)	HPMC-ES (5%, w/w)	Suspending in pre-concentrate by Cyclo-mixer (Suspension)	Solid su-SEDDS (Adsorption, calcium carbonate and talc)	-*In vivo* in Himalayan rabbits at a dose of 1 mg/kg, increase in C_{max} (3.4-fold) and AUC (2.7-fold) from solid su-SEDDS as compared with pure drug.	[116]
Griseofulvin (BCS II)	Oleic acid, Labrafil, Tween 20, Labrafac PG (5 mg/16.545 g)	Poloxamer (0.48%)	Adding in preconcentrate	Liquid	-PI effect: Poloxamer>HPMC -*In vivo* permeability in Wister rats at a dose of 1 ml, with a concentration of 0.05 mg/ml, three-fold more permeability through the intestine, compared with conventional SEDDS.	[169]

Table 5: Overview of approved anti-cancer nanodrugs

Name	Formula	Advanced indication (s)	References
Mepact	Liposomal mifamurtide	Osteosarcoma	[180]
Onivyde	Liposomal irinotecan	Pancreas ca	[181]
DaunoXome	Liposomal daunorubicin	HIV-related Kaposi sa	[191]
Caclyx,, Doxil	Pegylated liposomal doxorubicin	Breast, Ovarian ca, Kaposi sa, Mulitple myeloma	[190]
Oncaspar	PEG asparaginase	Acute lymphoblastic leukemia	[183]
DepoCyte	Liposomal cytarabine	Lymphomatousmeningosis	[192]
Marqibo	Liposomal vincristin	Acute lymphoblastic leukemia	[192]
Genexol	Paclitaxel loaded polymeric micelle	Breast, Pancreas ca, NSCLC	[186]
Abraxane	Albumin-bound paclitaxel	Breast, Pancreas ca, NSCLC	[193]
Kadcyla	Trastuzumab linked to emtansine	HER2+breast ca	[194]
Gliadel wafer	Carmustine in poliferosan 20	High grade glial tumors-local therapy	[195]

Suitable solid dosage forms for su-SEDDSs

Tablets

Solid su-SEDDSs can be mixed with other suitable excipients for the tableting; then, the mixture is compressed to a tablet using a compression machine. It is important to select a suitable combination of mixing excipients for tableting to prevent liquid SEDDS escape from the solid carrier by tableting pressure. Eutectic-based self-emulsifying tablets inhibit the irreversible precipitation of the drug within the formulation [106].

Implant

Some authors were reported that 1,3-bis(2-chloroethyl)-1-nitrosourea, a chemotherapeutic agent used to treat a malignant brain tumour, was formulated in SEDDS wafer implant to improve its effectiveness overcoming its short half-life and enhance its stability. These implants showed high *in vitro* antitumor activity and were less susceptible to hydrolysis as compared to that of PLGA [107].

Suppositories

A few papers demonstrated that solid SEDDS could enhance not only GI adsorption but also rectal/vaginal adsorption. For example, Glycyrrhizin, which barely achieves therapeutic plasma concentrations when administered via an oral route, can obtain satisfactory therapeutic levels for chronic hepatic diseases through either vaginal or rectal self-emulsifying suppositories [108].

Application of controlled-release technology in su-SEDDSs

The application of su-SEDDSs is mainly intended to improve the absorption of poorly water-soluble drugs, it would also be desirable to provide sustained-release action in the case of low-dose drugs with short biological half-lives that require frequent dosing [109, 110].

Solid S-SNEDDS

To improve the i) Stability, ii) Effective manufacturing cost, iii) Transportability, iv) Patient compliance, the liquid formulation (SNEDDS or S-SNEDDS) is converted into solid dosage form [111]. Their properties are given in table 6.

Table 6: Solid carriers and its properties

Solid carrier	Properties
Hydroxypropyl cellulose L type (HPC), low substituted hydroxypropyl cellulose B1 (L-HPC) and Vivapur 105 (used as cellulose-based diluents)	Have hydrophilic and viscous properties.
Neusilin US2, Florite PS-10, Sylysia 350 (used as silica-based adsorbents)	High surface area, high oil-absorption capacity, uniform pore size, and less particle size
Lactose monohydrate, Starch 1500 and maltodextrin (used as saccharide based diluents)	Have the ability to solubilize in water.

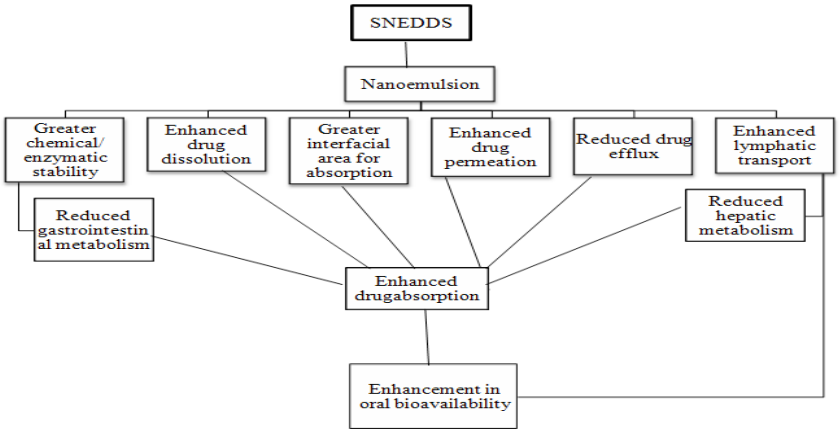

Fig. 5: Probables of SNEDDS (Reprinted from (124) with permission)

Self-double nanoemulsifying drug delivery systems (SDEDDS)

SDEDDS are a promising technology that could resolve this problem. These are w/o/w spontaneous emulsions that consist of hydrophilic surfactant and w/o emulsions where the w/o/w emulsions were spontaneously formed during dilution with water at mild agitation. SDEDDS are applicable for peptides, proteins, and other macromolecular drugs, such as, insulin [112-120].

Targeted SNEDDS

Nanoemulsion droplets have the ability to be maintained in the circulation for a long duration of time. Cationic nanoemulsions can also directly attach to the anionic membrane barriers [121-135].

Perspectives and future trends i

To estimate the feasibility of developing a su-SNEDDS candidate as a final drug product, it is very important to evaluate the formulation using an *in vitro* digestion model with a good IVIVC. Early *in vitro* studies emphasized solubilization; however, recent research has shifted this interest to drug supersaturation, as it is triggered by the dispersion and/or lipolysis of lipids. The increasing awareness of the potential of supersaturation as an enabling formulation approach for drugs suffering from solubility-limited absorption has stimulated the need for *in vivo* predictive supersaturation/precipitation assays. However, intragastric lipolysis is still overlooked, as it is in conventional *in vitro* lipolysis models. With regard to gastric lipolysis accounting for 5%–35% of *in vivo* lipolysis and the pH shift due to movement in the gastrointestinal tract, a two-compartment *in vitro* lipolysis model should be considered a priority method to get a better IVIVC. The importance of the selection of solidification excipients and methods for converting liquid su-SEDDSs to solid dosage forms is also mentioned in this review. Since most solidification studies have been conducted on conventional SEDDSs, further studies about the effect of PIs addition should be performed through the application of more drugs in various aspects. We hope this review will help develop a desired su-SEDDS for a model drug. It should also be beneficial for efficient research based on fundamental and experimental understanding, facilitating the insightful perspective of the reader.

CONCLUSION

Supersaturable-SEDDSs are a promising approach for the formulation of poorly water-soluble drugs to enhance their bioavailability through the induction and stabilization by PIs of a supersaturated drug state in the GI fluid. This approach overcomes the main limitations associated with conventional solubilized SEDDSs.

Su-SNEDDSs in particular shows great potential in enhancing aqueous solubility, stability, oral absorption and in minimizing inter/intra-patient dose variability. SNEDDSs improve the absorption of drugs by several pathways, including increasing membrane fluidity, bypassing the first-pass effect, and inhibition of P-gp efflux. These Su-SNEDDSs dispersion in the GI tract, nano-emulsions are formed, which facilitate oil hydrolysis by lipases on the oil–water interface. Following this process, micelles along with other colloidal structures made of phospholipids, bile salt, and triglycerides are formed, which increase the transport of the drug through the intestinal barrier. The submicron size of the system with enhanced surface activity allows more robust drug transport through the GI boundary layer, conclusively ensuing in superior drug absorption and a rapid onset of action and ease of manufacture and scale-up is one of the most important advantages that make unique when compared with other novel drug delivery systems, such as solid dispersions, liposomes and nanoparticles. To use supersaturable-SNEDDS for a target drug, it is important to understand the in-depth mechanism of precipitation through the supersaturation of the drug. From this, it may be possible to inhibit this precipitation and prolong supersaturation by considering the various factors that influence precipitation, based on this mechanism. Many anti-cancer, anti-diabetic, and anti-viral drug solubility, stability, and bioavailability characteristics were improved via SNEDDSs formulations. In spite of the advancements and conversions in su-SNEDDSs, there are still areas that commitment to be consigned to make su-SNEDDSs commercially gorgeous. The precedence of prospect research should be based on the mechanisms of action of different SNEDDSs formulations and pharmacokinetic studies, especially on human subjects.

FUNDING

Nil

CONFLICTS OF INTERESTS

The authors declare no conflict of interest.

AUTHORS CONTRIBUTIONS

All authors are contributed equally.

REFERENCES

1. Shah NH, Carvajal MT, Patel CI, Infeld MH, Malick AW. Self-emulsifying drug delivery systems (SEDDS) with polyglycolyzed glycerides for improving *in vitro* dissolution and oral absorption of lipophilic drugs. International Journal of Pharmaceutics. 1994;106(1):15-23. doi: 10.1016/0378-5173(94)90271-2.
2. Misal RS, Potphode VR, Mahajan VR. Review on: new approaches in self-micro-emulsifying drug delivery system. Res J Pharm Technol. 2017;10(4):1215-24. doi: 10.5958/0974-360X.2017.00218.9.
3. Singh B, Bandopadhyay S, Kapil R, Singh R, Katare O. Self-emulsifying drug delivery systems (SEDDS): formulation development, characterization, and applications. Crit Rev Ther Drug Carrier Syst. 2009;26(5):427-521. doi: 10.1615/critrevtherdrugcarriersyst.v26.i5.10, PMID 20136631.
4. Boyd BJ, Bergström CAS, Vinarov Z, Kuentz M, Brouwers J, Augustijns P, Brandl M, Bernkop-Schnurch A, Shrestha N, Preat V, Mullertz A, Bauer Brandl A, Jannin V. Successful oral delivery of poorly water-soluble drugs both depends on the intraluminal behavior of drugs and of appropriate advanced drug delivery systems. Eur J Pharm Sci. 2019;137:104967. doi: 10.1016/j.ejps.2019.104967.
5. Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharm Res. 1995;12(3):413-20. doi: 10.1023/a:1016212804288, PMID 7617530.
6. Danafar H, Rostamizadeh K, Hamidi M. Polylactide/poly(ethylene glycol)/polylactide triblock copolymer micelles as carrier for delivery of hydrophilic and hydrophobic drugs: a comparison study. J Pharm Investig. 2018;48(3):381-91. doi: 10.1007/s40005-017-0334-8.
7. Berthelsen R, Klitgaard M, Rades T, Müllertz A. In vitro digestion models to evaluate lipid-based drug delivery systems; present status and current trends. Adv Drug Deliv Rev. 2019;142:35-49. doi: 10.1016/j.addr.2019.06.010, PMID 31265861.
8. Chatterjee B, Hamed Almurisi S, Ahmed Mahdi Dukhan A, Mandal UK, Sengupta P. Controversies with self-emulsifying drug delivery system from the pharmacokinetic point of view. Drug Deliv. 2016;23(9):3639-52. doi: 10.1080/10717544.2016.1214990, PMID 27685505.
9. Dokania S, Joshi AK. Self-microemulsifying drug delivery system (SMEDDS)-challenges and road ahead. Drug Deliv. 2015;22(6):675-90. doi: 10.3109/10717544.2014.896058, PMID 24670091.
10. Burdock GA, Carabin IG. Generally recognized as safe (GRAS): history and description. Toxicol Lett. 2004;150(1):3-18. doi: 10.1016/j.toxlet.2003.07.004, PMID 15068820.
11. Joyce P, Dening TJ, Meola TR, Schultz HB, Holm R, Thomas N, Prestidge CA. Solidification to improve the biopharmaceutical performance of SEDDS: opportunities and challenges. Adv Drug Deliv Rev. 2019;142:102-17. doi: 10.1016/j.addr.2018.11.006, PMID 30529138.
12. Krishnaiah YS. Pharmaceutical technologies for enhancing oral bioavailability of poorly soluble drugs. J Bioeq Avail. 2010;2:28-36.
13. Rao SV, Shao J. Self-nano emulsifying drug delivery systems (SNEDDS) for oral delivery of protein drugs: I. Formulation development. Int J Pharm. 2008;362(1-2):2-9. doi: 10.1016/j.ijpharm.2008.05.018, PMID 18650038.
14. Kataoka M, Sugano K, da Costa Mathews C, Wong JW, Jones KL, Masaoka Y, Sakuma S, Yamashita S. Application of dissolution/Permeation system for evaluation of formulation effect on oral absorption of poorly water-soluble drugs in drug development. Pharm Res. 2012;29(6):1485-94. doi: 10.1007/s11095-011-0623-2, PMID 22134778.
15. Wei Y, Ye X, Shang X, Peng X, Bao Q, Liu M, Guo M, Li F. Enhanced oral bioavailability of silybin by a supersaturatable self-emulsifying drug delivery system (S-SEDDS). Colloids Surf Physicochem Eng Aspects. 2012;396:22-8. doi: 10.1016/j.colsurfa.2011.12.025.
16. Gao P, Akrami A, Alvarez F, Hu J, Li L, Ma C, Surapaneni S. Characterization an optimization of AMG 517 supersaturatable self-emulsifying drug delivery system (S-SEDDS) for improved oral absorption. J Pharm Sci. 2009;98(2):516-28. doi: 10.1002/jps.21451, PMID 18543293.
17. Thomas N, Holm R, Müllertz A, Rades T. *In vitro* and *in vivo* performance of novel supersaturated self-nanoemulsifying drug delivery systems (super-SNEDDS). J Control Release. 2012;160(1):25-32. doi: 10.1016/j.jconrel.2012.02.027, PMID 22405903.
18. Williams HD, Sassene P, Kleberg K, Calderone M, Igonin A, Jule E, Vertommen J, Blundell R, Benameur H, Müllertz A, Pouton CW, Porter CJ, LFCS Consortium. Toward the establishment of standardized *in vitro* tests for lipid-based formulations, part 3: understanding supersaturation versus precipitation potential during the *in vitro* digestion of type I, II, IIIA, IIIB and IV lipid-based formulations. Pharm Res. 2013;30(12):3059-76. doi: 10.1007/s11095-013-1038-z, PMID 23661145.
19. Suys EJA, Chalmers DK, Pouton CW, Porter CJH. Polymeric precipitation inhibitors promote fenofibrate supersaturation and enhance drug absorption from a type IV lipid-based formulation. Mol Pharm. 2018;15(6):2355-71. doi: 10.1021/acs.molpharmaceut.8b00206, PMID 29659287.
20. Ma X, Ma X, Williams RO. Polymeric nanomedicines for poorly soluble drugs in oral delivery systems: an update. J Pharm Investig. 2018;48:61-75.
21. Bandyopadhyay S, Katare OP, Singh B. Development of optimized Supersaturable self-nanoemulsifying systems of ezetimibe: effect of polymers and efflux transporters. Expert Opin Drug Deliv. 2014;11(4):479-92. doi: 10.1517/17425247.2014.877885, PMID 24386966.
22. Pouton CW. Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. Eur J Pharm Sci. 2006;29(3-4):278-87. doi: 10.1016/j.ejps.2006.04.016, PMID 16815001.
23. Brouwers J, Brewster ME, Augustijns P. Supersaturating drug delivery systems: the answer to solubility-limited oral bioavailability? J Pharm Sci. 2009;98(8):2549-72. doi: 10.1002/jps.21650, PMID 19373886.
24. Stillhart C, Kuentz M. Trends in the assessment of drug supersaturation and precipitation *in vitro* using lipid-based delivery systems. J Pharm Sci. 2016;105(9):2468-76. doi: 10.1016/j.xphs.2016.01.010, PMID 26935881.
25. Kuentz M. Drug supersaturation during formulation digestion, including real-time analytical approaches. Adv Drug Deliv Rev. 2019;142:50-61. doi: 10.1016/j.addr.2018.11.003, PMID 30445096.
26. Sinko PJ, Singh Y. Martin's physical pharmacy and pharmaceutical sciences: physical chemical and biopharmaceutical principles in the pharmaceutical sciences. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2011.
27. Ye J, Wu H, Huang C, Lin W, Zhang C, Huang B, Lu B, Xu H, Li X, Long X. Comparisons of *in vitro* Fick's first law, lipolysis, and *in vivo* rat models for oral absorption on BCS II drugs in SNEDDS. Int J Nanomedicine. 2019;14:5623-36. doi: 10.2147/IJN.S203911, PMID 31440045.
28. Warren DB, Benameur H, Porter CJH, Pouton CW. Using polymeric precipitation inhibitors to improve the absorption of poorly water-soluble drugs: a mechanistic basis for utility. J Drug Target. 2010;18(10):704-31. doi: 10.3109/1061186X.2010.525652, PMID 20973755.
29. Pouton CW. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and "self-microemulsifying' drug delivery systems. Eur J Pharm Sci. 2000;(11)11;Suppl 2:S93-8. doi: 10.1016/s0928-0987(00)00167-6, PMID 11033431.
30. Porter CJH, Trevaskis NL, Charman WN. Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs. Nat Rev Drug Discov. 2007;6(3):231–8231-48. doi: 10.1038/nrd2197, PMID 17330072.
31. Kashchiev D, Van Rosmalen GM. Review: Nucleation in solutions revisited. Cryst Res Technol. 2003;38(78):555-74. doi: 10.1002/crat.200310070.
32. Gao P, Shi Y. Characterization of supersaturable formulations for improved absorption of poorly soluble drug. AAPS Pharm Sci Tech. 2002;14(14):703-13.

33. Avdeef A. Absorption and drug development solubility, permeability and charge state. New York: Wiley- Interscience; 2003. p. 91-15.
34. Xu S, Dai WG. Drug precipitation inhibitors in supersaturable formulations. Int J Pharm. 2013;453(453):36-43. doi: 10.1016/j.ijpharm.2013.05.013, PMID 23680727.
35. Taylor LS, Zhang GGZ. Physical chemistry of supersaturated solutions and implications for oral absorption. Adv Drug Deliv Rev. 2016;101(101):122-42. doi: 10.1016/j.addr.2016.03.006, PMID 27013254.
36. Popov A, Schopf L, Bourassa J, Chen H. Enhanced pulmonary delivery of fluticasone propionate in rodents by mucus-penetrating nanoparticles. Int J Pharm. 2016;502(1-2):188-97. doi: 10.1016/j.ijpharm.2016.02.031, PMID 26902722.
37. Amin OM, Ammar A, Eladawy SA. Febuxostat loaded β-cyclodextrin based nanosponge tablet: an *in vitro* and *in vivo* evaluation. J Pharm Investig. 2020;50(4):399-411. doi: 10.1007/s40005-019-00464-w.
38. Rodriíguez Hornedo N, Murphy D. Significance of controlling crystallization mechanisms and kinetics in pharmaceutical systems. J Pharm Sci. 1999;88(7):651-60. doi: 10.1021/js980490h, PMID 10393562.
39. Warren DB, Benameur H, Porter CJH, Pouton CVW. Using polymeric precipitation inhibitors to improve the absorption of poorly water-soluble drugs: a mechanistic basis for utility. J Drug Target. 2010;18(10):704-31. doi: 10.3109/1061186X.2010.525652, PMID 20973755.
40. Da Costa Mathews C, Sugano K. Supersaturable formulations. Drug Deliv Syst. 2010;25(4):371-4. doi: 10.2745/dds.25.371.
41. Chen ZQ, Liu Y, Zhao JH. Improved oral bioavailability of poorly water-soluble indirubin by a supersaturatable self-microemulsifying drug delivery system. Int J Nanomedicine. 2012;7:1115-25.
42. Park H, Ha ES, Kim MS. Current status of supersaturable self-emulsifying drug delivery systems. Pharmaceutics. 2020;12(4):365. doi: 10.3390/pharmaceutics12040365, PMID 32316199.
43. Niu B, Singh V, Zhou Y, Wu CY, Pan X, Wu CQuan G, Niu B, Singh V, Zhou Y, Wu CY, Pan X, Wu C. Supersaturable solid self-microemulsifying drug delivery system: precipitation inhibition and bioavailability enhancement. Int J Nanomed.icine. 2017;12:8801-11. doi: 10.2147/IJN.S149717, PMID 29263669.
44. Bandyopadhyay S, Katare OP, Singh B. Development of optimized supersaturable self-nanoemulsifying systems of ezetimibe: effect of polymers and efflux transporters. Expert Opin Drug Deliv. 2014;11(4):479-92. doi: 10.1517/17425247.2014.877885, PMID 24386966.
45. Ujhelyi Z, Vecsernyés M, Feher P, Kosa D, Arany P, Nemes D, Sinka D, Vasvari G, Fenyvesi F, Varadi J, Bacskay I. Physico-chemical characterization of self-emulsifying drug delivery systems. Drug Discov Today Technol. 2018;(27)27:81–-6. doi: 10.1016/j.ddtec.2018.06.005, PMID 30103867.
46. Patil P, Joshi P, Paradkar A. Effect of formulation variables on preparation and evaluation of gelled self-emulsifying drug delivery system (SEDDS) of ketoprofen. APS PharmSciTech. 2004;5(3):43–50e42. doi: 10.1208/pt050342, PMID 15760075.
47. Gershanik T, Benita S. Self-dispersing lipid formulations for improving oral absorption of lipophilic drugs. Eur J Pharm Biopharm, Elsevier B. V. Amsterdam, the Netherlands. 2000;50(1):179-88. doi: 10.1016/s0939-6411(00)00089-8, PMID 10840200.
48. Nazzal S, Smalyukh II, Lavrentovich OD, Khan MA. Preparation and *in vitro* characterization of a eutectic-based semisolid self-Nano emulsified drug delivery system (SNEDDS) of ubiquinone: mechanism and progress of emulsion formation. Int J Pharm. 2002;235(1-2):247-65. doi: 10.1016/s0378-5173(02)00003-0, PMID 11879759.
49. Ujhelyi Z, Vecsernyes M, Feher P, Kosa D, Arany P, Nemes D, Sinka D, Vasvari G, Fenyvesi F, Varadi J, Bacskay I. Physico-chemical characterization of self-emulsifying drug delivery systems. Drug Discov Today Technol. 2018;27:81-6. doi: 10.1016/j.ddtec.2018.06.005, PMID 30103867.
50. Pouton CW, Charman WN. The potential of oily formulations for drug delivery to the gastrointestinal tract. Adv Drug Deliv Rev. 1997;25(1):1-2. doi: 10.1016/S0169-409X(96)00486-3.
51. Amala FK, Boby JG, Jeny S, Vinod B, Sunil C. A review on self emulsifying nanoemulsion. J Pharm Res. 2017;1(4): 1-17.
52. Bolzinger Thevenin MA, Grossiord JL, Poelman MC. Characterization of a sucrose ester microemulsion by freeze-fracture electron micrograph and small-angle neutron scattering experiments. Langmuir. 1999;15(7):2307-15. doi: 10.1021/la9804278.
53. Angell CA, Kadiyala RK, MacFarlane DR. Glass-forming microemulsions. J Phys Chem. 1984;88(20):4593-6. doi: 10.1021/j150664a031.
54. Barker SA, Craig DQM, Taylor KMG, Hill RM. The study of liposomes by low-frequency dielectric spectroscopy. J Pharm Pharmacol Suppl. 1989;41:1.
55. Craig D. An investigation into the mechanisms of self-emulsification using particle size analysis and low-frequency dielectric spectroscopy. International Journal of Pharmaceutics. 1995;114(1):103-10. doi: 10.1016/0378-5173(94)00222-Q.
56. Gershanik T, Benita S. Self-dispersing lipid formulations for improving oral absorption of lipophilic drugs Elsevier BV. Amsterdam, The Netherlands. 2000;50:179-88.
57. Breitkreitz MC, Sabin GP, Polla G, Poppi RJ. Characterization of semi-solid self-emulsifying drug delivery systems (SEDDS) of atorvastatin calcium by Raman image spectroscopy and chemometrics. J Pharm Biomed Anal. 2013;73:3-12. doi: 10.1016/j.jpba.2012.03.054, PMID 22522036.
58. Abdalla A, Mader K. Preparation and characterization of a self-emulsifying pellet formulation. Eur J Pharm Biopharm. 2007;66(2):220-6. doi: 10.1016/j.ejpb.2006.11.015, PMID 17196807.
59. Sonawale P, Patil A, Kamble A, Bhutkar M. Solubility enhancement of lipophilic drugs-solid self micro-emulsifying drug delivery system. Asian J Pharm Technol. 2016;6(3):155. doi: 10.5958/2231-5713.2016.00022.2.
60. Rahman MA, Hussain A, Hussain MS, Mirza MA, Iqbal Z. Role of excipients in the successful development of self-emulsifying/microemulsifying drug delivery system (SEDDS/SMEDDS). Drug Dev Ind Pharm. 2013;39(1):1-19. doi: 10.3109/03639045.2012.660949, PMID 22372916.
61. Feeney OM, Crum MF, McEvoy CL, Trevaskis NL, Williams HD, Pouton CW, Charman WN, Bergström CAS, Porter CJH. 50 y of oral lipid-based formulations: Provenance, progress and future perspectives,. Adv Drug Deliv Rev.. 2016;101:167-94. doi: 10.1016/j.addr.2016.04.007, PMID 27089810.
62. Williams HD, Trevaskis NL, Yeap YY, Anby MU, Pouton CW, Porter CJH. Lipid-based formulations and drug supersaturation: harnessing the unique benefits of the lipid digestion/absorption pathway. Pharm Res. 2013;30(12):2976-92. doi: 10.1007/s11095-013-1126-0, PMID 23824582.
63. Stillhart C, Kuentz M. Trends in the assessment of drug supersaturation and precipitation *in vitro* using lipid-based delivery systems. J Pharm Sci. 2016;105(9):2468-76. doi: 10.1016/j.xphs.2016.01.010, PMID 26935881.
64. Fatouros DG, Nielsen FS, Douroumis D, Hadjileontiadis LJ, Mullertz A. *In vitro–in vivo* correlations of self-emulsifying drug delivery systems combining the dynamic lipolysis model and neuro-fuzzy networks. Eur J Pharm Biopharm. 2008;69(3):887-98. doi: 10.1016/j.ejpb.2008.01.022, PMID 18367386.
65. Birru WA, Warren DB, Headey SJ, Benameur H, Porter CJH, Pouton CW, Chalmers DK. Computational models of the gastrointestinal Environment. 1. The effect of digestion on the phase behavior of intestinal fluids. Mol Pharm. 2017;14(3):566-79. doi: 10.1021/acs.molpharmaceut.6b00888, PMID 28099023.
66. Suys EJA, Warren DB, Porter CJH, Benameur H, Pouton CW, Chalmers DK. Computational models of the intestinal Environment. 3. The impact of cholesterol content and pH on mixed micelle colloids. Mol Pharm. 2017;14(11):3684-97. doi: 10.1021/acs.molpharmaceut.7b00446, PMID 28980815.
67. Mosgaard MD, Sassene PJ, Mu H, Rades T, Müllertz A. High-throughput lipolysis in 96-well plates for rapid screening of lipid-based drug delivery systems. J Pharm Sci. 2017;106(4):1183-6. doi: 10.1016/j.xphs.2016.12.026, PMID 28057543.
68. Mosgaard MD, Sassene P, Mu H, Rades T, Müllertz A. Development of a high-throughput *in vitro* intestinal lipolysis

model for rapid screening of lipid-based drug delivery systems. Eur J Pharm Biopharm. 2015;94:493-500. doi: 10.1016/j.ejpb.2015.06.028, PMID 26159837.
69. Keemink J, Maartensson E, Bergstroom CAS. Lipolysis-permeation setup for simultaneous study of digestion and absorption *in vitro*. Mol Pharm. 2019;16(3):921-30. doi: 10.1021/acs.molpharmaceut.8b00811, PMID 30628771.
70. Alskar LC, Parrow A, Keemink J, Johansson P, Abrahamsson B, Bergström CAS. Effect of lipids on absorption of carvedilol in dogs: is coadministration of lipids as efficient as a lipid-based formulation? J Control Release. 2019;304:90-100. doi: 10.1016/j.jconrel.2019.04.038, PMID 31047962.
71. Crum MF, Trevaskis NL, Williams HD, Pouton CW, Porter CJH. A new in vitro lipid digestion-*in vivo* absorption model to evaluate the mechanisms of drug absorption from lipid-based formulations. Pharm Res. 2016;33(4):970-82. doi: 10.1007/s11095-015-1843-7, PMID 26703975.
72. Nikolakakis I, Partheniadis I. Self-emulsifying granules and pellets: Composition and formation mechanisms for instant or controlled release. Pharmaceutics. 2017;9(4):50. doi: 10.3390/pharmaceutics9040050, PMID 29099779.
73. Tan A, Rao S, Prestidge CA. Transforming lipid-based oral drug delivery systems into solid dosage forms: an overview of solid carriers, physicochemical properties, and biopharmaceutical performance. Pharm Res. 2013;30(12):2993-3017. doi: 10.1007/s11095-013-1107-3, PMID 23775443.
74. Warren DB, Benameur H, Porter CJ, Pouton CW. Using polymeric precipitation inhibitors to improve the absorption of poorly water-soluble drugs: A mechanistic basis for utility. J Drug Target. 2010;18(10):704-31. doi: 10.3109/1061186X.2010.525652, PMID 20973755.
75. Kaur G, Chandel P, Hari Kumar SL. Formulation development of self-Nano emulsifying drug delivery system (SNEDDS) of celecoxib for improvement of oral bioavailability. Pharmacophore. 2013;4(4):120-5.
76. Yahaya ZS, Oyi AR, Allagh TS, Abdulsamad A. Development and characterization of self-nano emulsifying drug delivery system of ibuprofen. J Pharma Res Int. 2018;23(2):1-31. doi: 10.9734/JPRI/2018/43090.
77. Quan G, Niu B, Singh V, Zhou Y, Wu CY, Pan X, Wu C. Supersaturable solid self-micro emulsifying drug delivery system: precipitation inhibition and bioavailability enhancement. Int J Nanomedicine. 2017;12(8801).
78. Dokania S, Joshi AK. Self-micro emulsifying drug delivery system (SMEDDS)-challenges and road ahead. Drug Deliv. 2015;22(6):675-90. doi: 10.3109/10717544.2014.896058, PMID 24670091.
79. Chae GS, Lee JS, Kim SH, Seo KS, Kim MS, Lee HB, Khang G. Enhancement of the stability of BCNU using self-emulsifying drug delivery systems (SEDDS) and *in vitro* antitumor activity of self-emulsified BCNU-loaded PLGA wafer. Int J Pharm. 2005;301(1-2):6-14. doi: 10.1016/j.ijpharm.2005.03.034, PMID 16024190.
80. Kim JY, Ku YS. Enhanced absorption of indomethacin after oral or rectal administration of a self-emulsifying system containing indomethacin to rats. Int J Pharm. 2000;194(1):81-9. doi: 10.1016/s0378-5173(99)00367-1, PMID 10601687.
81. Lee KH, Park C, Oh G, Park JB, Lee BJ. New blends of hydroxypropyl methylcellulose and gelucire 44/14: physical property and controlled release of drugs with different solubility. J Pharm Investig. 2018;48(3):313-21. doi: 10.1007/s40005-017-0322-z.
82. Dawaba HM, Dawaba AM. Development and evaluation of extended-release ciprofloxacin HCl ocular inserts employing natural and synthetic film-forming agents. J Pharm Investig. 2019;49(2):245-57. doi: 10.1007/s40005-018-0400-x.
83. Hajjar B, Zier KI, Khalid N, Azarmi S, Lobenberg R. Evaluation of a micro emulsion-based gel formulation for topical drug delivery of diclofenac sodium. J Pharm Investig. 2018;48(3):351-62. doi: 10.1007/s40005-017-0327-7.
84. Singh D, Bedi N, Tiwary AK. Enhancing solubility of poorly aqueous soluble drugs: critical appraisal of techniques. J Pharm Investig. 2018;48(5):509-6. doi: 10.1007/s40005-017-0357-1.
85. Tan A, Rao S, Prestidge CA. Transforming lipid-based oral drug delivery systems into solid dosage forms: an overview of solid carriers, physicochemical properties, and biopharmaceutical performance. Pharm Res. 2013;30(12):2993-3017. doi: 10.1007/s11095-013-1107-3, PMID 23775443.
86. Anton N, Vandamme TF. The universality of low-energy nano-emulsification. Int J Pharm. 2009;377(1-2):142-7. doi: 10.1016/j.ijpharm.2009.05.014, PMID 19454306.
87. Sadurní N, Solans C, Azemar N, Garcia-Celma MJ. Studies on the formation of O/W nano-emulsions by low-energy emulsification methods suitable for pharmaceutical applications. Eur J Pharm Sci. 2005;26(5):438-45. doi: 10.1016/j.ejps.2005.08.001, PMID 16153811.
88. Porter CJ, Trevaskis NL, Charman WN. Lipids and lipid-based formulations: Ooptimizing the oral delivery of lipophilic drugs. Nat Rev Drug Discov. 2007;6(3):231-48. doi: 10.1038/nrd2197, PMID 17330072.
89. Gade AV, Salunkhe KS, Chaudhari SR, Gadge PB, Dighe GS, Amit Asati A. Review on, self-micro emulsifying drug delivery system. Am J Pharm Tech Res. 2015;5(1):51-66.
90. Pallavi M, Nigade SL, Patil Shradha S, Tiwari. Self-emulsifying drug delivery system (SEDDS)-a review. Int J Pharm Biol Sci. 2012;2(2):42-52.
91. Biradar SV, Dhumal RS, Paradkar AR. Rheological Iinvestigation of Sself-emulsification process: effect of co-surfactant. J Pharm Pharm Sci. 2009;12(2):164-74. doi: 10.18433/j3qc7x, PMID 19732494.
92. Do Thi TD, Van Speybroeck M, Barillaro V, Martens J, Annaert P, Augustijns P, Van Humbeeck J, Vermant J, Van den Mooter G. Formulate-ability of ten compounds with different physicochemical profiles in SMEDDS. Eur J Pharm Sci. 2009;38(5):479-88. doi: 10.1016/j.ejps.2009.09.012, PMID 19782131.
93. Gao P, Shi Y. Characterization of supersaturatable formulations for improved absorption of poorly soluble drugs. AAPS J. 2012;14(4):703-13. doi: 10.1208/s12248-012-9389-7, PMID 22798021.
94. Mu H, Holm R, Mullertz A. Lipid-based formulations for oral administration of poorly water-soluble drugs. Int J Pharm. 2013;453(1):215-24. doi: 10.1016/j.ijpharm.2013.03.054, PMID 23578826.
95. Li P, Hynes SR, Haefele TF, Pudipeddi M, Royce AE, Serajuddin AT. Development of clinical dosage forms for a poorly water-soluble drug II: Formulation and characterization of a novel solid microemulsion preconcentrate system for oral delivery of a poorly water-soluble drug. J Pharm Sci. 2009;98(5):1750-64. doi: 10.1002/jps.21547, PMID 18781639.
96. Serajuddin A, Li P, Haefele T. Development of lipid-based drug delivery systems for poorly water-soluble drugs as viable oral dosage forms-present status and future prospects. Am Pharm Rev. 2008;11:34-42.
97. Chen ZQ, Liu Y, Zhao JH, Wang L, Feng NP. Improved oral bioavailability of poorly water-soluble indirubin by a supersaturatable self-micro emulsifying drug delivery system. International J Nanomedicine. 2012;7:1115-25. doi: 10.2147/IJN.S28761, PMID 22403491.
98. Bevernage J, Hens B, Brouwers J, Tack J, Annaert P, Augustijns P. Supersaturation in human gastric fluids. Eur J Pharm Biopharm. 2012;81(1):184-9. doi: 10.1016/j.ejpb.2012.01.017, PMID 22342777.
99. Miller DA, DiNunzio JC, Yang W, McGinity JW, Williams RO. Enhanced in vivo absorption of itraconazole via stabilization of supersaturation following acidic-to-neutral pH transition. Drug Dev Ind Pharm. 2008;34(8):890-902. doi: 10.1080/03639040801929273, PMID 18608468.
100. Ilevbare GA, Liu H, Edgar KJ, Taylor LS. Understanding polymer properties important for crystal growth inhibition—impact of chemically diverse polymers on solution crystal growth of ritonavir. Cryst Growth Des. 2012;12(6):3133-43. doi: 10.1021/cg300325p.
101. Xie S, Poornachary SK, Chow PS, Tan RBH. Direct precipitation of micronsize salbutamol sulfate: new insights into the action of surfactants and polymeric additives. Cryst Growth Des. 2008;10(8):3363-70.
102. Plaizier Vercammen JA. Interaction of povidone with aromatic compounds IV: effects of macromolecule molecular weight,

solvent dielectric constant, and ligand solubility on complex formation. J Pharm Sci. 1983;72(9):1042-4. doi: 10.1002/jps.2600720920, PMID 6631691.
103. Garekani HA, Ford JL, Rubinstein MH, Rajabi-Siahboomi AR. Highly compressible paracetamol: I: crystallization and characterization. Int J Pharm. 2000;208(1-2):87-99. doi: 10.1016/s0378-5173(00)00550-0, PMID 11064214.
104. Palmelund H, Madsen CM, Plum J, Mullertz A, Rades T. Studying the propensity of compounds to supersaturate: a practical and broadly applicable approach. J Pharm Sci. 2016;105(10):3021-9. doi: 10.1016/j.xphs.2016.06.016, PMID 27488902.
105. Friesen DT, Shanker R, Crew M, Smithey DT, Curatolo WJ, Nightingale JA. Hydroxypropyl methylcellulose acetate succinate-based spray-dried dispersions: an overview. Mol Pharm. 2008;5(6):1003-19. doi: 10.1021/mp8000793, PMID 19040386.
106. Overhoff KA, McConville JT, Yang W, Johnston KP, Peters JI, Williams RO. Effect of stabilizer on the maximum degree and extent of supersaturation and oral absorption of tacrolimus made by ultra-rapid freezing. Pharm Res. 2008;25(1):167-75. doi: 10.1007/s11095-007-9417-y, PMID 17968635.
107. Rodriguez CH, Scamehorn JF. Kinetics of precipitation of surfactants. II. Anionic surfactant mixtures. J Surfact Deterg. 2001;4(1):15-26. doi: 10.1007/s11743-001-0156-6.
108. Dai WG, Dong LC, Li S, Deng ZY. Combination of pluronic/vitamin E TPGS as a potential inhibitor of drug precipitation. Int J Pharm. 2008;355(1-2):31-7. doi: 10.1016/j.ijpharm.2007.12.015, PMID 18299178.
109. Loftsson T, Vogensen SB, Brewster ME, Konraodsdottir F. Effects of cyclodextrins on drug delivery through biological membranes. J Pharm Sci. 2007;96(10):2532-46. doi: 10.1002/jps.20992, PMID 17630644.
110. Dash RN, Mohammed H, Humaira T. Design, optimization, and evaluation of ezetimibe solid supersaturatable self-nano emulsifying drug delivery for enhanced solubility and dissolution. J Pharma Investig. 2016 Apr 1;46(2):153-68. doi: 10.1007/s40005-015-0225-9.
111. Shanmugam S, Baskaran R, Balakrishnan P, Thapa P, Yong CS, Yoo BK. Solid self-nanoemulsifying drug delivery system (S-SNEDDS) containing phosphatidylcholine for enhanced bioavailability of highly lipophilic bioactive carotenoid lutein. Eur J Pharma Biopharma. 2011;79(2):250-7. doi: 10.1016/j.ejpb.2011.04.012, PMID 21550401.
112. Seo YG, Kim DW, Yousaf AM, Park JH, Chang PS, Baek HH, Lim SJ, Kim JO, Yong CS, Choi HG. Solid self-nanoemulsifying drug delivery system (SNEDDS) for enhanced oral bioavailability of poorly water-soluble tacrolimus: physicochemical characterization and pharmacokinetics. J Microencapsul. 2015;32(5):503-10. doi: 10.3109/02652048.2015.1057252, PMID 26079598.
113. Yeom DW, Chae BR, Kim JH, Chae JS, Shin DJ, Kim CH, Kim SR, Choi JH, Song SH, Oh D, Sohn SI, Choi YW. Solid formulation of a supersaturable self-microemulsifying drug delivery system for valsartan with improved dissolution and bioavailability. Oncotarget. 2017;8(55):94297-316. doi: 10.18632/oncotarget.21691, PMID 29212229.
114. Date AA, Nagarsenker MS. Design and evaluation of self-nanoemulsifying drug delivery systems (SNEDDS) for cefpodoxime proxetil. Int J Pharm. 2007;329(1-2):166-72. doi: 10.1016/j.ijpharm.2006.08.038, PMID 17010543.
115. Wang L, Dong J, Chen J, Eastoe J, Li X. Design and optimization of a new self-nanoemulsifying drug delivery system. J Colloid Interface Sci. 2009;330(2):443-8. doi: 10.1016/j.jcis.2008.10.077, PMID 19038395.
116. Rege BD, Kao JPY, Polli JE. Effects of nonionic surfactants on membrane transporters in caco-2 cell monolayers. Eur J Pharm Sci. 2002;16(4-5):237-46. doi: 10.1016/s0928-0987(02)00055-6, PMID 12208453.
117. Dixit RP, Nagarsenker MS. Formulation and in vivo evaluation of self-nanoemulsifying granules for oral delivery of a combination of ezetimibe and simvastatin. Drug Dev Ind Pharm. 2008;34(12):1285-96. doi: 10.1080/03639040802071570, PMID 18720144.
118. Srikanth Reddy S, Suresh Gande S. A comprehensive review on self-nano emulsifying drug delivery systems: advancements and applications. Int J Pharm Sci and Drug Res. 2020;12(5):1-8.
119. Yamashita K, Nakate T, Okimoto K, Ohike A, Tokunaga Y, Ibuki R, Higaki K, Kimura T. Establishment of new preparation method for solid dispersion formulation of tacrolimus. Int J Pharm. 2003;267(1-2):79-91. doi: 10.1016/j.ijpharm.2003.07.010, PMID 14602386.
120. Zhang N, Zhang W, Jin Y, Quan DQ. Studies on preparation of carbamazepine (CBZ) supersaturate self-micro emulsifying (S-SMEDDS) formulation and relative bioavailability in beagle dogs. Pharm Dev Technol. 2011;16(4):415-21. doi: 10.3109/10837451003774419, PMID 20433250.
121. Tajarobi F, Larsson A, Matic H, Abrahmsen-Alami S. The influence of crystallization inhibition of HPMC and HPMCAS on model substance dissolution and release in swellable matrix tablets. Eur J Pharm Biopharm. 2011;78(1):125-33. doi: 10.1016/j.ejpb.2010.11.020, PMID 21168491.
122. Tian F, Saville DJ, Gordon KC, Strachan CJ, Zeitler JA, Sandler N, Rades T. The influence of various excipients on the conversion kinetics of carbamazepine polymorphs in aqueous suspension. J Pharm Pharmacol. 2007;59(2):193–20193-201. doi: 10.1211/jpp.59.2.0006, PMID 17270073.
123. Chauhan H, Hui-Gu C, Atef E. Correlating the behavior of polymers in solution as precipitation inhibitor to its amorphous stabilization ability in solid dispersions. J Pharm Sci. 2013;102(6):1924-35. doi: 10.1002/jps.23539, PMID 23580406.
124. Curatolo W, Nightingale JA, Herbig SM. Utility of hydroxypropylmethylcellulose acetate succinate (HPMCAS) for initiation and maintenance of drug supersaturation in the GI milieu. Pharm Res. 2009;26(6):1419-31. doi: 10.1007/s11095-009-9852-z, PMID 19277850.
125. Bi M, Kyad A, Kiang YH, Alvarez Nunez F, Alvarez F. Enhancing and sustaining AMG 009 dissolution from a matrix tablet via microenvironmental pH modulation and supersaturation. AAPS PharmSciTech. 2011;12(4):1157-62. doi: 10.1208/s12249-011-9679-x, PMID 21913050.
126. Brewster ME, Vandecruys R, Peeters J, Neeskens P, Verreck G, Loftsson T. Comparative interaction of 2-hydroxypropyl-β-cyclodextrin and sulfobutylether-β-cyclodextrin with itraconazole: phase-solubility behavior and stabilization of supersaturated drug solutions. Eur J Pharm Sci. 2008;34(2-3):94-103. doi: 10.1016/j.ejps.2008.02.007, PMID 18420390.
127. Muthu MS, Feng SS. Pharmaceutical stability aspects of nanomedicines. Nanomedicine (Lond). 2009;4(8):857-60. doi: 10.2217/nnm.09.75, PMID 19958220.
128. Wang X, Jiang S, Wang X, Liao J, Yin Z. Preparation and evaluation of nnattokinase-loaded self-double-emulsifying drug delivery system. Asian J Pharm Sci. 2015;10(5):386-95. doi: 10.1016/j.ajps.2015.04.005.
129. Shima M, Tanaka M, Fujii T, Egawa K, Kimura Y, Adachi S, Matsuno R. Oral administration of insulin included in fine W/O/W emulsions to rats. Food Hydrocoll. 2006;20(4):523-31. doi: 10.1016/j.foodhyd.2005.05.002.
130. Hoormann K, Zimmer A. Drug delivery and drug targeting with parenteral lipid nanoemulsions- A review. J Control Release. 2016;223:85-98. doi: 10.1016/j.jconrel.2015.12.016, PMID 26699427.
131. Nikonenko B, Reddy VM, Bogatcheva E, Protopopova M, Einck L, Nacy CA. Therapeutic efficacy of SQ641-NE against mycobacterium tuberculosis mycobacterium tuberculosis. Antimicrob Agents Chemother. 2014;58(1):587-9. doi: 10.1128/AAC.01254-13, PMID 24145521.
132. Hunter AC, Elsom J, Wibroe PP, Moghimi SM. Polymeric particulate technologies for oral drug delivery and targeting: a pathophysio-logicalpathophysiological perspective. Nanomedicine: Nanotechnology Biology and Medicine. 2012;(8)8:S5-20S5-S20. doi: 10.1016/j.nano.2012.07.005.
133. Siena S, Doebele RC, Shaw AT, Karapetis CS, Tan DS, Cho BC, Kim D, Ahn M, Krebs M, Goto K, Garrido Lopez P, Farago AF, Loong HHF, Tosi D, Barve MA, Simmons BP, Ye C, Eng S, Drilon AE. Efficacy of entrectinib in patients (PTS) with solid tumors and central nervous system (CNS) metastases: integrated analysis from three clinical trials. J Clin Oncol. 2019;(37)37(15_Suppl):3017. doi: 10.1200/JCO.2019.37.15_suppl.3017.

134. Merz V, Zecchetto C, Melisi D. Pemigatinib, A potent inhibitor of FGFRs for the treatment of cholangiocarcinoma. Future Oncol. 2021;17(4):389-402. doi: 10.2217/fon-2020-0726, PMID 33034201.
135. Hoy SM. Pemigatinib: first approval. Drugs. 2020;80(9):923-9. doi: 10.1007/s40265-020-01330-y, PMID 32472305.
136. Abou-Alfa GK, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, Paulson AS, Borad MJ, Gallinson D, Murphy AG, Oh DY, Dotan E, Catenacci DV, Van Cutsem E, Ji T, Lihou CF, Zhen H, Féliz L, Vogel A. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: A multicentre, open-label, phase 2 study. Lancet Oncol. 2020;21(5):671-84. doi: 10.1016/S1470-2045(20)30109-1, PMID 32203698.
137. Romero D. Benefit from pemigatinib in cholangiocarcinoma. Nat Rev Clin Oncol. 2020;17(6):337. doi: 10.1038/s41571-020-0369-z, PMID 32300194.
138. Singh G, Pai RS. *In vitro* and *in vivo* performance of supersaturable self-nanoemulsifying system of trans-resveratrol. Artif Cells Nanomed Biotechnol. 2016;44(2):510-6. doi: 10.3109/21691401.2014.966192, PMID 25331709.
139. Tung NT, Tran CS, Nguyen HA, Nguyen TD, Chi SC, Pham DV, Bui QD, Ho XH. Formulation and biopharmaceutical evaluation of supersaturatable self-nanoemulsifying drug delivery systems containing silymarin. Int J Pharm. 2019;555:63-76. doi: 10.1016/j.ijpharm.2018.11.036, PMID 30448315.
140. Lee DR, Ho MJ, Jung HJ, Cho HR, Park JS, Yoon SH, Choi YS, Choi YW, Oh CH, Kang MJ. Enhanced dissolution and oral absorption of tacrolimus by supersaturable self-emulsifying drug delivery system. Int J Nanomed.icine. 2016;11:1109-17. doi: 10.2147/IJN.S102991, PMID 27051286.
141. Shin DJ, Chae BR, Goo YT, Yoon HY, Kim CH, Sohn SI, Oh D, Lee A, Song SH, Choi YW. Improved dissolution and oral bioavailability of valsartan using a solidified supersaturable self-microemulsifying drug delivery system containing gelucire® 44/14/14. Pharmaceutics. 2019;(11)11(2):58. doi: 10.3390/pharmaceutics11020058, PMID 30708963.
142. Kim MS, Ha ES, Choo GH, Baek IH. Preparation and *in vivo* evaluation of a dutasteride-loaded solid-supersaturatable self-microemulsifying drug delivery system. Int J Mol Sci. 2015;16(5):10821-33. doi: 10.3390/ijms160510821, PMID 25984604.
143. Lee DH, Yeom DW, Song YS, Cho HR, Choi YS, Kang MJ, Choi YW. Improved oral absorption of dutasteride via Soluplus®-based supersaturable self-emulsifying drug delivery system (S-SEDDS). Int J Pharm. 2015;478(1):341-7. doi: 10.1016/j.ijpharm.2014.11.060, PMID 25437113.
144. Zheng D, Lv C, Sun X, Wang J, Zhao Z. Preparation of a supersaturatable self-microemulsion as drug delivery system for ellagic acid and evaluation of its antioxidant activities. J Drug Deliv Sci Technol. 2019;53. doi: 10.1016/j.jddst.2019.101209.
145. Jaisamut P, Wiwattanawongsa K, Graidist P, Sangsen Y, Wiwattanapatapee R. Enhanced oral bioavailability of curcumin using a supersaturatable self-microemulsifying system incorporating a hydrophilic polymer; *in vitro* and *in vivo* investigations. APS PharmSciTech. 2018;19(2):730-40. doi: 10.1208/s12249-017-0857-3, PMID 28975598.
146. Lee DR, Ho MJ, Choi YW, Kang MJ. A polyvinylpyrrolidone-based supersaturable self-emulsifying drug delivery system for enhanced dissolution of cyclosporine a. Polymers. 2017;9(4):124. doi: 10.3390/polym9040124, PMID 30970802.
147. Anby MU, Williams HD, McIntosh M, Benameur H, Edwards GA, Pouton CW, Porter CJ. Lipid digestion as a trigger for supersaturation: evaluation of the impact of supersaturation stabilization on the in vitro and in vivo performance of self-emulsifying drug delivery systems. Mol Pharm. 2012;9(7):2063-79. doi: 10.1021/mp300164u, PMID 22656917.
148. Chen Y, Chen C, Zheng J, Chen Z, Shi Q, Liu H. Development of a solid supersaturatable self-emulsifying drug delivery system of docetaxel with improved dissolution and bioavailability. Biol Pharm Bull. 2011;34(2):278-86. doi: 10.1248/bpb.34.278, PMID 21415541.
149. Baek Ih B, Ha ES, Yoo JW, Jung Y, Kim MS. Design of a gelatin microparticle containing self-microemulsifying formulation for enhanced oral bioavailability of dutasteride. Drug Des Dev Ther. 2015;9:323.
150. Shi Y, Gao P, Gong Y, Ping H. Application of a biphasic test for characterization of *in vitro* drug release of immediate release formulations of celecoxib and its relevance to *in vivo* absorption. Mol Pharm. 2010;7(5):1458-65. doi: 10.1021/mp100114a, PMID 20704265.
151. Chavan RB, Modi SR, Bansal AK. Role of solid carriers in pharmaceutical performance of solid supersaturable SEDDS of celecoxib. Int J Pharm. 2015;495(1):374-84. doi: 10.1016/j.ijpharm.2015.09.011, PMID 26364711.
152. Song WH, Yeom DW, Lee DH, Lee KM, Yoo HJ, Chae BR, Song SH, Choi YW. In situ intestinal permeability and in vivo oral bioavailability of celecoxib in supersaturating self-emulsifying drug delivery system. Arch Pharmacal Res. 2014;37(5):626-35. doi: 10.1007/s12272-013-0202-7, PMID 23852645.
153. Gao P, Rush BD, Pfund WP, Huang T, Bauer JM, Morozowich W, Kuo MS, Hageman MJ. Development of a supersaturable SEDDS (S-SEDDS) formulation of paclitaxel with improved oral bioavailability. J Pharm Sci. 2003;92(12):2386-98. doi: 10.1002/jps.10511, PMID 14603484.
154. Gao P, Guyton ME, Huang T, Bauer JM, Stefanski KJ, Lu Q. Enhanced oral bioavailability of a poorly water soluble drug PNU-91325 by supersaturatable formulations. Drug Dev Ind Pharm. 2004;30(2):221-9. doi: 10.1081/ddc-120028718, PMID 15089057.
155. Chen ZQ, Liu Y, Zhao JH, Wang L, Feng NP. Improved oral bioavailability of poorly water-soluble indirubin by a supersaturatable self-microemulsifying drug delivery system. Int J Nanomed.icine. 2012;7:1115-25. doi: 10.2147/IJN.S28761, PMID 22403491.
156. Dash RN, Mohammed H, Humaira T, Reddy AV. Solid supersaturatable self-nanoemulsifying drug delivery systems for improved dissolution, absorption and pharmacodynamic effects of glipizide. J Drug Deliv Sci Technol. 2015;28:28-36. doi: 10.1016/j.jddst.2015.05.004.
157. Zadeha BSM, Salimi A, Aminib R. Novel super saturated self-emulsifying system for oral delivery of griseofulvin: design, preparation and ex-vivo intestinal permeability. J Rep Pharm Sci. 2017;6:180-90.
158. Araujo JM, Gomez AC, Pinto JA, Rolfo C, Raez LE. Profile of entrectinib in the treatment of ROS1-positive non-small cell lung cancer: evidence to date. Hematol Oncol Stem Cell Ther. 2021;14(3):192-8. doi: 10.1016/j.hemonc.2020.11.005. PMID 33290717.
159. Ardini E, Menichincheri M, Banfi P, Bosotti R, De Ponti C, Pulci R, Ballinari D, Ciomei M, Texido G, Degrassi A, Avanzi N, Amboldi N, Saccardo MB, Casero D, Orsini P, Bandiera T, Mologni L, Anderson D, Wei G, Harris J, Vernier JM, Li G, Felder E, Donati D, Isacchi A, Pesenti E, Magnaghi P, Galvani A. Entrectinib, a Pan-TRK, ROS1, and ALK inhibitor with activity in multiple molecularly defined cancer indications. Mol Cancer Ther. 2016;15(4):628-39. doi: 10.1158/1535-7163.MCT-15-0758, PMID 26939704.
160. Liu D, Offin M, Harnicar S, Li BT, Drilon A. Entrectinib: an orally available, selective tyrosine kinase inhibitor for the treatment of NTRK, ROS1, and ALK fusion-positive solid tumors. Ther Clin Risk Manag. 2018;14:1247-52. doi: 10.2147/TCRM.S147381, PMID 30050303.
161. Drilon A, Sankhala KK, Liu SV, Cho BC, Blakely C, Chee CE. STARTRK-2: A global phase 2, open-label, basket study of entrectinib in patients with locally advanced or metastatic solid tumors harboring TRK, ROS1, or ALK gene fusions. Cancer Res. 2017;77:CT060.
162. Mah PT, Novakovic D, Saarinen J, Van Landeghem S, Peltonen L, Laaksonen T, Isomaki A, Strachan CJ. Elucidation of compression-Induced surface crystallization in amorphous tablets using sum frequency generation (SFG) microscopy. Pharm Res. 2017;34(5):957-70. doi: 10.1007/s11095-016-2046-6, PMID 27738954.
163. Loftsson T. The effect of water-soluble polymers on aqueous solubility of drugs. International Journal of Pharmaceutics. 1996;127(2):293-6. doi: 10.1016/0378-5173(95)04207-5.
164. Lindfors L, Forssen S, Westergren J, Olsson U. Nucleation and crystal growth in supersaturated solutions of a model drug. J

Colloid Interface Sci. 2008;325(2):404-13. doi: 10.1016/j.jcis.2008.05.034, PMID 18561941.
165. Rosenthal E, Poizot Martin I, Saint Marc T, Spano JP, Cacoub P, DNX Study Group, DNX Study Group. Phase IV study of liposomal daunorubicin (DaunoXome) in AIDS-related Kaposi sarcoma. Am J Clin Oncol. 2002 Feb;25(1):57-9. doi: 10.1097/00000421-200202000-00012, PMID 11823698.
166. Petre CE, Dittmer DP. Liposomal daunorubicin as treatment for Kaposi''s sarcoma. Int J Nanomedicine. 2007;2(3):277-88. PMID 18019828.
167. Ando K, Mori K, Corradini N, Redini F, Heymann D. Mifamurtide for the treatment of nonmetastatic osteosarcoma. Ex opinion on. Pharmacotherapy. 2011;12(2):285-92.
168. Frampton JE. Liposomal irinotecan: a review in metastatic pancreatic adenocarcinoma drugs. Drugs. 2020;80(10):1007-18. doi: 10.1007/s40265-020-01336-6, PMID 32557396.
169. Lyseng Williamson KA, Duggan ST, Keating GM. Pegylated liposomal doxorubicin: a guide to its use in various malignancies. BioDrugs. 2013 Oct;27(5):533-40. doi: 10.1007/s40259-013-0070-1, PMID 24018470.
170. Vieira Pinheiro JP, Müller HJ, Schwabe D, Gunkel M, Casimiro da Palma J, Henze G, von Schutz V, Winkelhorst M, Würthwein G, Boos J. Drug monitoring of low-dose PEG-asparaginase (Oncaspar) in children with relapsed acute lymphoblastic leukaemia. Br J Haematol. 2001 Apr;113(1):115-9. doi: 10.1046/j.1365-2141.2001.02680.x, PMID 11328290.
171. Kripp M, Hofheinz RD. Treatment of lymphomatous and leukemic menin-gitis with liposomal encapsulated cytarabine. International Journal of Nanomedicine. 2008;3(4):97-401.
172. Shah NN, Merchant MS, Cole DE, Jayaprakash N, Bernstein D, Delbrook C, Richards K, Widemann BC, Wayne AS. Vincristine sulfate liposomes injection (VSLI, Marqibo®): results from a Phase I study in children, adolescents, and young adults with refractory solid tumors or leukemias. Pediatr Blood Cancer. 2016 Jun;63(6):997-1005. doi: 10.1002/pbc.25937, PMID 26891067.
173. Shea JE, Nam KH, Rapoport N, Scaife CL. Genexol inhibits primary tumour growth and metastases in gemcitabine-resistant pancreatic ductal adenocarcinoma adenocarcinoma. Int Hepato Pan Biliary Assoc. 2011;13(3):153-7.
174. Yardley DA. Nab-paclitaxel mechanisms of action and delivery. J Control Release. 2013;170(3):365-72. doi: 10.1016/j.jconrel.2013.05.041, PMID 23770008.
175. Squires H, Stevenson M, Simpson E, Harvey R, Stevens J. Trastuzumab emtansine for ttreating HER2-positive, unresectable, locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane: an evidence review group perspective of a NICE single technology appraisal. Pharmacoeconomics. 2016;34(7):673-80. doi: 10.1007/s40273-016-0386-z, PMID 26892972.
176. Kleinberg L. Polifeprosan 20, 3.85% carmustine slow-release wafer in malignant glioma: evidence for role in era of standard adjuvant temozolomide. Core Evidence. 2012;7:115-30. doi: 10.2147/CE.S23244, PMID 23118709.
177. Duggan ST, Keating GM. Pegylated liposomal doxorubicin: a review of its use in metastatic breast cancer, ovarian cancer, multiple myeloma and AIDS-related Kaposi''s sarcoma. Drugs. 2011 Dec 24;71(18):2531-58. doi: 10.2165/11207510-000000000-00000, PMID 22141391.
178. Gonçalves PH, Uldrick TS, Yarchoan R. HIV-associated Kaposi sarcoma and related diseases. AIDS. 2017;31(14):1903-16. doi: 10.1097/QAD.0000000000001567, PMID 28609402.
179. Raj TA, Smith AM, Moore AS. Vincristine sulfate liposomal injection for acute lymphoblastic leukemia. Int J Nanomedicine. 2013;8:4361-9. doi: 10.2147/IJN.S54657, PMID 24232122.
180. IRinehart J, Adjei AA, Lorusso PM, Waterhouse D, Hecht JR, Natale RB, Hamid O, Varterasian M, Asbury P, Kaldjian EP, Gulyas S, Mitchell DY, Herrera R, Sebolt-Leopold JS, Meyer MB. Multicenter phase II study of the oral MEK inhibitor, CI-1040, in patients with advanced non-small-cell lung, breast, colon, and pancreatic cancer. J Clin Oncol. 2004 Nov 15;22(22):4456-62. doi: 10.1200/JCO.2004.01.185, PMID 15483017.
181. Von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, Wolmark N, Rastogi P, Schneeweiss A, Redondo A, Fischer HH, Jacot W, Conlin AK, Arce-Salinas C, Wapnir IL, Jackisch C, DiGiovanna MP, Fasching PA, Crown JP, Wülfing P, Shao Z, Rota Caremoli E, Wu H, Lam LH, Tesarowski D, Smitt M, Douthwaite H, Singel SM, Geyer CE Jr;, KATHERINE Investigators. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med. 2019;380(7):617-28. doi: 10.1056/NEJMoa1814017, PMID 30516102.
182. Talibi SS, Talibi SS, Aweid B, Aweid O. Prospective therapies for high-grade glial tumours: A literature review. Annals of Med Surg (Lond). 2014;3(3):55-9. doi: 10.1016/j.amsu.2014.04.003, PMID 25568787.
183. Cimino C. Essential oils: pharmaceutical applications and encapsulation strategies into lipid-based delivery systems." Pharmaceutics Vol. 2021;13(3):327.
184. Regina Brigelius Flohe R, Frank J Kelly FJ, Jukka T Salonen JT, Jiri Neuzil J, Jean-Marc Zingg JM, Angelo Azzi A. The European perspective on vitamin E: current knowledge and future research. The American Journal of Clinical Nutrition. 2002;76(4):703-16. doi: 10.1093/ajcn/76.4.703, PMID 12324281.
185. Alshamsan A, Kazi M, Badran MM, Alanazi FK. Role of alternative lipid eexcipients in the design of self-nanoemulsifying formulations for fenofibrate: characterization, *in vitro* dispersion, digestion and ex vivo gut permeation studies. Frontiers in Pharmacology. 2018;9:1219. doi: 10.3389/fphar.2018.01219, PMID 30455642.
186. Praful D. Role components in the formation of self-microemulsifying drug delivery systems. Ind J Pharm Sci. 2015;77(3):249-57.
187. Hamid KM, Wais M, Sawant G. A review on nanoemulsions: formulation, composition, and applications. Asian J Pharm Clin Res. 2021;14:22-8. doi: 10.22159/ajpcr.2021.v14i4.40859.
188. Charman WN, Porter CJ, Mithani S, Dressman JB. Physiochemical and physiological mechanisms for the effects of food on drug absorption: the role of lipids and pH. J Pharm Sci. 1997;86(3):269-82. doi: 10.1021/js960085v, PMID 9050793.
189. Sonia Anand S, Rishikesh Gupta R, Prajapati SKSk P. Self-microemulsifying drug delivery system. Asian J Pharm Clin Res. 2016;9:33-8. doi: 10.22159/ajpcr.2016.v9s2.13180.
190. Pelletta MA, Castellano S, Hadgraft J, Davis AF, Castellanob S, Hadgrafta J, Davisc AF. The penetration of supersaturated solutions of piroxicam across silicone membranes and human skin *in vitro*. Journal of Controlled Release. 1997;46(3):205-14. doi: 10.1016/S0168-3659(96)01595-7.
191. Quan G, Niu B, Singh V, Zhou Y, Wu CY, Pan X, Wu C. Supersaturable solid self-microemulsifying drug delivery system: precipitation inhibition and bioavailability enhancement. International Journal of Nanomedicine. 2017;12:8801-11. doi: 10.2147/IJN.S149717, PMID 29263669.
192. David E, Alonzo DE, Raina S, Zhou D, Gao Y, Zhang GGZ, Taylor LSAlonzo DE, Raina S, Zhou D, Gao Y, Zhang GGZ, Taylor LS. Characterizing the impact of hydroxypropylmethyl cellulose on the growth and nucleation kinetics of felodipine from supersaturated solutions. Cryst Growth Des. 2012;12(3):1538-47. doi: 10.1021/cg201590j.
193. Kumar A, Sharma S, Kamble R. Self-emulsifying drug delivery system (SEDDS): future aspects. Int J Pharm Pharm Sci. 2010;2:7-13.
194. Mistry R, Sheth NS. Self-emulsifying drug delivery system. Int J Pharm Pharm Sci. 2011;3:23-8.
195. Agueros M, Zabaleta V, Espuelas S, Campanero MA, Irache JM. Increased oral bioavailability of paclitaxel by its encapsulation through complex formation with cyclodextrins in poly(anhydride) nanoparticles. J Control Release. 2010;145(1):2-8. doi: 10.1016/j.jconrel.2010.03.012. PMID 20347897.
196. Zadeha BSM, Salimi A, Aminib R. Novel super saturated self-emulsifying system for oral delivery of griseofulvin: design, preparation and ex-vivo intestinal permeability. Journal of Reports in Pharmaceutical Sciences. 2017;6(2):180-90.
197. Lee DR, Ho MJ, Choi YW, Kang MJ. A polyvinylpyrrolidone-based supersaturable self-emulsifying drug delivery system for

enhanced dissolution of cyclosporine a. Polymers. 2017;9(4):1-11. doi: 10.3390/polym9040124, PMID 30970802.

198. Jackson MJ, Kestur US, Hussain MA, Taylor LS,. Dissolution of danazol amorphous solid dispersions: supersaturation and phase behavior as a function of drug loading and polymer type. Mol Pharm Pharm. 2016;13(1):223-31. doi: 10.1021/acs.molpharmaceut.5b00652, PMID 26618718.
199. Sugihara H, Taylor LS. Evaluation of pazopanib phase behavior following ph-induced supersaturation. Mol Pharmaceutics 2018;15(4):1690-9. doi: 10.1021/acs.molpharmaceut.8b00081, PMID 29502424.