

Self-Nanoemulsifying Systems in Modern Therapeutics: A Clinically Established and Commercially Proven Drug delivery strategy

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ABSTRACT

A low solubility in aqueous solution has been a significant obstacle in designing orally administered drugs, especially those drugs of BCS Class II and IV. To address these shortcomings, Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) have become a potent platform to increase solubilization, fast nanoemulsion formation, and membrane permeability and lymphatic uptake. This review provides an extensive international discussion of SNEDDS application, with reference to their mechanistic benefits, technological developments, and proven clinical results. Widespread usage in such regions as the United States, Europe, Japan, India and Brazil all indicate an improving acceptance by regulations and market trust. It has been extensively illustrated in clinical reports that SNEDDS improve bioavailability, decrease interpatient variability in pharmacokinetics and improve therapeutic responses in a variety of drug classes, e.g. immunosuppressant, antiretroviral, cardiovascular agents, oncology drugs, CNS therapeutics, antidiabetic, and phytochemicals. Also, such innovations as SNEDDS solid, SNEDDS supersaturated, and hybrid nano-lipid systems have enhanced stability and compliance of the formulations among the other innovations. Major issues still lie in the safety of excipients, scalability of manufacturing, environmental friendliness and alignment of global regulatory standards. However, overall evidence proves that SNEDDS can be described as a universal, efficient, and internationally relevant approach to the enhancement of oral medication availability. The current development in the science of formulation and the alignment of the regulations will increase the clinical and commercial implications of SNEDDS in contemporary therapeutics further.

Keywords: Self-Nanoemulsifying Drug Delivery Systems (SNEDDS); lipid-based formulations; bioavailability enhancement,

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INTRODUCTION

Poor water solubility of drugs continues to pose a significant challenge to the pharmaceutical industrial landscape globally in terms of delivering poorly water soluble drugs especially those in the Biopharmaceutical Classification System (BCS) Class II and IV, where dissolution and permeability inhibitors are key factors that limit oral bio-availability[1]. Over 40-percent of the new drug entrant's fall under such categories as specified, that's why solubility improvement is among the main priorities in the science of drug delivery. To overcome this dilemma, lipid-based drug delivery system (LBDDS) has become one of the most encouraging formulation methods as the Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) has captured much of the international interest owing to its high efficiency and adaptability in formulation [2]. The SNEDDS are oils, surfactants and co-solvents isotropic mixtures which form spontaneously at the gastrointestinal tract and into fine oil-in-water nanoemulsions when the mixture comes under mild agitation [3]. It is a spontaneous nanoemulsification,

which yields droplets between 20 and 200 nm in size, in effect, increasing surface area, increasing dissolution rate, and increasing the consistency of drug absorption.

The property of SNEDDS to keep the drugs in a solubilized form during their passage in the gastrointestinal system is deemed as one of the main points of their success in the clinics [4].

The clinical usefulness of SNEDDS is in the fact that they surmount several barriers related to biopharmaceuticals at a concurrent time-solubility, permeability, efflux transport, and first-pass metabolism. A number of studies prove that SNEDDS formulations have the potential to restrain mechanisms of P-glycoprotein (P-gp) efflux and promote uptake of lymphatic's thus enhancing systemic exposure and minimizing inter-subject differences in pharmacokinetic profiles [5]. These characteristics render SNEDDS especially appropriate to drugs that have low and unpredictable oral bioavailability, small therapeutic indices, and drugs that need fast action initiation. The adoption of SNEDDS technology has grown considerably in the past 20 years across the world. The

use of SNEDDS in approved pharmaceutical products has been embraced in other regions including Europe, the United States, Japan, and India, which is a testimony that SNEDDS has regulatory acceptance all over the world [6]. The commercial SNEDDS preparations, including cyclosporine, ritonavir, and fenofibrate, prove the topology of the conversion of the laboratory progress to the practical clinical environment [7]. These are clinically tested products which can be considered as the important points of reference as they provide evidence that SNEDDS can positively influence pharmacokinetic parameters besides improving therapeutic effects, dose stability and patient adherence. The SNEDDS technology continues with innovation even in the global arena. The new ones are to be supersaturated SNEDDS (s-SNEDDS), solid SNEDDS (S-SNEDDS), or hybrid nano-systems incorporating polymeric or inorganic carriers to enhance stability, and to control release properties [8]. These improvements contain the long-standing challenges, including formulation precipitation, excipient toxicity issues, and environmental sensitivity during the production and storage. Global use of SNEDDS is affected by areas

such as regulatory needs, OE requirements, manufacturability of scales and regional technology capacity despite its benefits. However, the ongoing growth of SNEDDS-related clinical trials indicates the increased trust in pharmaceutical industries and medical systems all over the world. The SNEDDS formulations are in line with global health requirements, especially when it comes to chronic diseases (cardiovascular disease, infectious diseases, metabolic diseases, oncology, and immunosuppression) [9]. Owing to the growing need to have effective means of oral delivery of poorly soluble therapeutics, it is important to know how SNEDDS are used globally and evidence that it has received clinical validation as a successful delivery tool. This review is a compilation of the trends within the world, views on regulations, technological advances and compiles clinical results that expand on the importance of SNEDDS in the current pharmaceutical development. Through analysis of clinically proven examples and trends of adoption worldwide, the paper identifies SNEDDS as a revolutionary drug delivery technology with massive current and future effects on healthcare across the world [10].

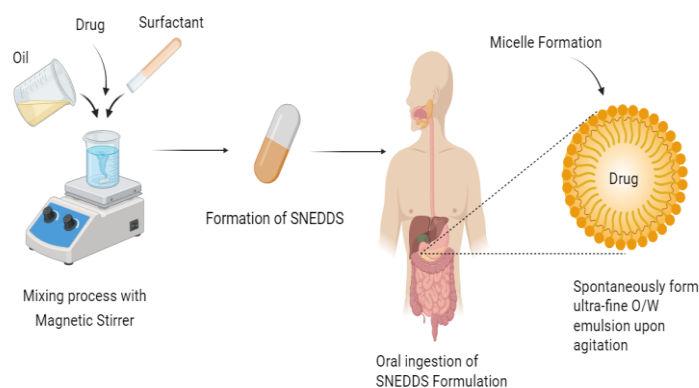


Figure 1. Basic components and SNEDDS formation with mild agitation within GIT

2. Components of Self Nano-emulsifying Drug Delivery System

Oils/Lipids (glycerides)

Oils are a paramount constituent of SNEDDS, as they not only have the inclination to optimized the drug uptake via intestinal lymphatic system to eventually maximize its acquisition from the digestive canal but also exhibiting a high solubilization potential for lipophilic active ingredients formulated as a SNEDDS. Oils role as a carrier or vehicle for transporting the drug in SNEDDS can be partitioned into modified medium- and long chain triglycerides of varying drug loading efficiency or hydrolytic cleavage. These glycerides have increased payload capacity, better emulsification profile when combined with a suitable solubilizing surfactant, and their degradation products are similar to the natural end products of intestinal digestion [12, 19]. Natural, unmodified edible oils might seem to be a rational option for SEDDS development; however, these are inefficient in dissolving a high lipophilic drug load and

possess inept self-emulsification properties [20]. Currently, lipidic systems utilize mono-, di-, and triglycerides, alongside fatty acid esters of propylene glycol in various formulations. Both saturated and unsaturated fatty acids are common, with SNEDDS specifically containing saturated fatty acids such as caproic, caprylic, capric, lauric, and myristic acid. These semi-synthetic lipid components are amphiphilic and contribute surfactant-like properties [21]. The lipid constituents in SNEDDS include mono-, di-, or triglyceryl derivatives with HLB values from 1 to 6. Mixtures of these glycerides with fatty acid esters of polyethylene glycol (PEG), which have HLB values between 3 and 18, can also be used to fabricate SNEDDS [22]. Oils are essential in SNEDDS as they carry lipophilic drugs, improve solubility, promote lymphatic transport, and enhance drug absorption.

Surfactants/ Emulsifying agents

Surfactants are essential in Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) as they lower the interfacial tension between oil and water, leading to

stable emulsions. They function as emulsifiers, regulating droplet size, release rate, and system stability [24]. Non-ionic surfactants function as P-glycoprotein efflux inhibitors by blocking the ATP-binding cassette and improve drug absorption by disrupting membrane packing in the gastrointestinal lumen, facilitating passive transport through the gut wall [26]. Surfactants for SNEDDS are selected based on safety and HLB profiles, with high HLB values indicating greater aqueous affinity. This characteristic is essential for improving the self-emulsifying properties of lipidic drug delivery systems, facilitating rapid o/w droplet formation and dispersion in aqueous environments [27]. Efficient drug absorption in the gut can be facilitated by holding the drug at the absorption site for an extended period, preventing precipitation [28]. Compared to ionic surface active agents, non-ionic surfactants are thought to be safer and can stabilize systems throughout the physiological pH range and ionic strengths which can affect the stability and droplet of nanoemulsion [29, 30]. Examples of surfactants used in preparation of SNEDDS are Tweens, Cremphor CL, Cremphor RH 40, Labrasol, Labrafil (M2125CS) etc.

For SNEDDS, the surfactant concentration should be 30-60% to prevent gastric mucosa irritation and cytotoxicity. Higher concentrations may be necessary for dissolving hydrophobic drugs, but using a mixture of surfactants can enhance solubilization efficiency and reduce the total surfactant quantity needed for an effective self-emulsifying system [29]. Surfactants enhance emulsification by reducing interfacial tension, stabilize formulations, improve drug absorption by inhibiting efflux mechanisms, and facilitate the rapid formation of fine oil-in-water droplets in the gastrointestinal tract.

Co-surfactant/Co-solvents

SNEDDS utilize hydrophilic surfactants to dissolve hydrophobic drug substances, supported by co-surfactants such as medium to short-chain alcohols (e.g., polyethylene glycol, propylene glycol). These co-surfactants enhance emulsification by improving fluidity between emulsion phases and preventing liquid crystallization, making them suitable for oral drug delivery [31]. The selection of a co-surfactant depends on its ability to enhance the emulsification area alongside the surfactant. Both components preferentially adsorb at the interface, creating a mechanical barrier against coalescence and lowering interfacial energy, which boosts the thermodynamic stability of the emulsion by reducing the overall energy of the system [32]. The selection of surfactants and co-surfactants for effective SNEDDS should prioritize emulsification efficiency over low solubilizing capacity for hydrophobic drugs. Co-surfactants enhance emulsification, thermodynamic stability, and minimize drug precipitation, promoting consistent drug delivery and absorption [32, 36]

Drugs

Frequently, drug falling under BCS Classes II and IV having low solubility and low permeability respectively, making them notorious candidates for the formulation to

overcome poor oral absorption, though not all drugs are suitable. Additionally, addressing drug sedimentation in the gastrointestinal tract is crucial in SNEDDS design [37]. In SEDDS formulations, it is recommended that the log P of drugs should be greater than 5 for optimal solubility in lipid, surfactant, and co-surfactant phases. Compounds with a log P above 2 typically show adequate solubility, improving absorption potential [38, 39]. Selecting appropriate drugs for SNEDDS is crucial for enhancing solubility, improving absorption, and focuses on the drug maintaining its strength and producing the desired biological effect.

REVIEW PAPER

Table1. Currently investigated SNEDDS formulations worldwide

Drugs (year)	Oils	Surfactants	Co-surfactant	Solid carrier	Key outcomes	Ref.
Cannabidiol (2025)	Medium chain triglycerides (MCT 10%)	Labrasol (36%) + Tween 80 (36%)	Transcutol-P (18%)	Fujicalin® SG – adsorption method and Calcium silicate – spray drying method.	Both liquid and solid SNEDDS showed excellent performance with liquid SNEDDS releasing nearly all drug quickly and faster absorption and greater systemic exposure.	1
Carvedilol (2025)	Pecol (25%)	Tween 80 (50%)	Labrasol (25%)	Mesoporous silica nanoparticles (MSNs)	In this study 400-fold increase in solubility, ~5.7-fold increase in dissolution at 60 minutes, AUC increased by ~21.7 times, Cmax increased by ~15.7 times compared to pure carvedilol	2
Cyproterone acetate (2025)	Tea tree oil	Tween 80	PEG 400	-	The optimized SNEDDS (SCT3) having Particle size: 125 ± 5 nm, Polydispersity index (PDI): 0.15 ± 0.01, Zeta potential: -25 ± 2 mV, ~90% CPA release & ~75% permeation across biological membranes conforming promising delivery system for water insoluble drugs.	3
Curcumin	Caproyl PGMC (15%)	Tween 80(55%)	Transcutol-P (28%)	-	This study investigates curcumin (CUR)-loaded self-nanoemulsifying drug delivery systems as a topical ocular delivery strategy to improve CUR's poor solubility, low bioavailability, and instability having droplet size < 50 nm, nearly 100% transmittance (high clarity), high curcumin loading and Sustained release for 48 hours. Ultimately enhanced cellular uptake of CUR in retinal cells.	4
Curcumin	Jasmine oil	Cremphore RH 40	-	GranuLac® 200 Tablettose® 80 FlowLac® 100	This study successfully developed a solid SNEDDS particle size after redispersion: 44.97–75.27 nm, Low polydispersity index (PDI), indicating uniform and homogeneous	5

					nanoemulsion droplets, Zeta potential: +0.31 to +1.25 mV. The developed S-SNEDDS effectively enhanced the solubility and improve the oral bioavailability of curcumin.	
Buckwheat flavonoids	Castor oil	PEG-40 hydrogenated castor oil	Propylene glycol	-	The optimized SNEDDS formulation of buckwheat flavonoids: Improved physicochemical characteristics like - particle size: ~23 nm, Polydispersity index (PDI): ~0.22, Zeta potential: ~-20.9 mV, Encapsulation efficiency ~98% and better in vitro release ~88% and also enhances their low oral bioavailability and solubility, providing increased antioxidant and antimicrobial activity.	6
Atorvastatin	Oleic acid	Tween 80	Span 60	Wall material (lactose, mannitol, pectin) and also used chitosan as coating agent for development of chitosan coated SNEDDS.	The simple and chitosan-decorated SNEDDS were solidified by spray drying using pectin as a matrix former to produce nanoemulsion-loaded microspheres. Among the formulations, the chitosan-decorated solidified SNEDDS (SF10) demonstrated superior physicochemical properties, favorable morphological characteristics, and enhanced aerodynamic performance compared with SF8, making it suitable for the systemic delivery of atorvastatin. The chitosan-decorated solidified SNEDDS achieved a dispersed fraction of 85% with a mass median aerodynamic diameter (MMAD) of 1.24 µm, supporting a higher fine particle fraction (FPF) of 54% when administered via a HANDIHALER®. The developed solidified SNEDDS represent a promising alternative platform for the	7

						systemic pulmonary delivery of atorvastatin.	
Dexibuprofen (2009)	Labrafil M 1944 CS	Labrasol	Capryol 90	Aerosil 200 (colloidal silicon dioxide; inert carrier used for spray drying)		The study provide droplet size of 224 ± 19 nm and showed improved pharmacokinetic parameters (C_{max} , AUC) also achieved $\sim 2\times$ bioavailability enhancement compared with plain drug powder.	8
Meloxicam (2023)	Peppermint oil (PO) and Medium-chain triglyceride (MCT); Optimized PO:MCT ratio = 1.78 : 1	Span 80 + Tween 80 (HLB ≈ 14)	PEG 400	Mannitol; Fumed Silica (Lyophilization)		The optimized MX-PO-SNEDDS showed a particle size of 47 ± 3 nm, a stability index of 85 ± 4 %, an ex-vivo flux of 4 ± 0.6 $\mu\text{g}/\text{cm}^2/\text{min}$, and a low ulcer index of 1 ± 0.25 %, indicating good stability, enhanced permeation, and reduced gastrointestinal irritation. MX-SNELCs showed disintegration time of 3 ± 1 s, and 91% drug release within 60 min; pharmacokinetic studies in humans demonstrated higher C_{max} , improved T_{max} , increased AUC, and bioavailability of 152.97% (~ 1.53 -fold) compared with marketed meloxicam tablets.	9
Azithromycin (2017)	Caproyl 90 and octanoic acid	Tween and span 80	Transcutol	Aerosil 200		The purpose of study is to improved solubility and dissolution rate, helping address the main causes of azithromycin's low oral bioavailability. Evaluation parameters. The prepared SENDDS formulation showed the droplet size: <150 nm, Transmittance: $>85\%$ (in DW, 0.1 mM HCl, and SIF), Dissolution: After 5 min, Liquid SEDDS: $>90\%$ drug release, Solid SEDDS: $\sim 52\%$ release; where the pure drug showed $\sim 11\%$	10

REVIEW PAPER

Furosemide (2024)	Oleic acid	Tween 80, Cremophor EL, Tween 20	PEG 400	Microcrystalline cellulose (MCC)	The developed liquid and solid SNEDDS of furosemide showed similar droplet sizes after dilution (about 115–116 nm). The solid SNEDDS exhibited improved enzymatic stability, showing 1.8-fold less lipase-mediated degradation than the liquid system. Drug-release studies revealed rapid release from liquid SNEDDS (≈90% in 30 min), whereas the solid SNEDDS provided sustained release (≈63% over 180 min). In vivo diuretic studies in mice demonstrated that liquid SNEDDS produced a rapid and higher urine output, while solid SNEDDS produced a slower but sustained diuretic effect. Overall, although liquid SNEDDS enhanced solubility and rapid onset, solid SNEDDS offered better stability, reduced degradation, sustained release, and a more predictable therapeutic response.	11
Celecoxib (2022)	Miglyol® 812	Gelucire® 44/14	Tween® 80 & d-TPGS	Calcium silicate (Zeopharm® 600), silicon dioxide (Aeroperl® 300 Pharma, Sipernat® 160 PQ, Syloid® XDP 3050), and cellulose (Avicel® PH-101, M-MC, and M-GA) were used as carrier/absorbent.	A spray-dried cellulose–gum arabic microparticulate carrier was identified as the most suitable adsorptive material for converting liquid SNEDDS into solid SNEDDS without affecting drug release, owing to its spherical morphology and good drug content and release. This carrier showed promising drug-loading and release performance and may serve as an alternative platform for formulating poorly soluble drugs, warranting further optimization and evaluation with other SNEDDS systems.	12, 13

REVIEW PAPER

Glimepiride (2015)	Miglyol 812	Tween 80	PEG 400	Aerosol 200	An optimized glimepiride S-SNEDDS was successfully developed, producing a fine nanoemulsion with narrow droplet size and converting the drug into an amorphous/molecularly dispersed state. The formulation showed faster dissolution and higher bioavailability (increased AUC) than pure glimepiride, indicating its potential as an effective dosage form for maintaining blood glucose levels.	14
Amomum compactum essential oil - 10%	Virgin coconut oil- 10%	Tween 80	PEG 400	-	A self-nanoemulsifying drug delivery system (SNEDDS) of <i>Amomum compactum</i> (cardamom) essential oil was successfully developed using an optimized mixture design. The formulation produced very small droplets (~14 nm), high transmittance, rapid emulsification, and good thermodynamic stability, resulting in improved solubility and stability of the essential oil and showing potential antibacterial use as an alternative to antibiotics in poultry	15
Resveratrol	Capryol 90	Cremophor EL	Tween 20	-	An optimized resveratrol SNEDDS developed of Capryol 90, Cremophor EL, and Tween 20 produced nano-sized droplets (~41 nm) and increased oral bioavailability by 3.2-fold compared with plain resveratrol. The formulation also showed significant anti-fatigue effects, including faster lactate recovery, reduced ammonia levels, increased glucose, and longer swimming time to exhaustion, indicating improved	16

					exercise performance and therapeutic potential.	
Ramipril	Capmul MCM	HCO-30	Transcutol	Syloid 244 FP	The study successfully developed a solid self-nanoemulsifying tablet (T-SNEDDS) of Ramipril (RMP) to overcome its major formulation challenges, including poor aqueous solubility, degradation in lipid-based systems, and sensitivity to heat, moisture, and mechanical stress. Among six liquid formulations prepared according to the Lipid Formulation Classification System (LFCS), the optimized L-SNEDDS formulation F5 demonstrated high drug loading, small droplet size, and high negative zeta potential, indicating good nanoemulsion stability. Overall, developed Ramipril-loaded T-SNEDDS, it is a superior alternative to conventional formulations of Ramipril.	17
Methotrexate (2019)	Ethyl oleate	Tween® 80	Propylene glycol	-	The study successfully developed SMEDDS loaded with methotrexate showed with a mean droplet size of 39.42nm. In vitro drug release in different pH media showed that the release profile of MTX from the MTX/ β -CD loaded SMEDDS was influenced by the pH of the release medium and presented the characteristics of a sustained release profile. C _{max} increased 1.57 and 1.68-fold, respectively compared to native drug.	18
Darunavir	Lauroglycol® 90	Tween® 80	Transcutol® HP	-	In this research, successful development of the SNEDDS of Darunavir showed globule size of the OPT-D-SNEOFs was found to be	19

50.01 nm and the zeta potential found to be – 22.1 mV. The concentration of drug in formulation, i.e., 31.625 μ M, was found to be safe and enhancement in AUC_{0-t}, oral bio-availability and C_{max}, 1.45, 5.8 and 7.5-fold, respectively compared to free drug.

3. MECHANISMS BEHIND CLINICAL SUCCESS OF SNEDDS

The clinical efficacy of Self-Nanoemulsifying Drug Delivery System (SNEDDS) is because of various interrelationships between biopharmaceutical and physiological processes that work synergistically to degrade drug solubility, absorption, and systemic availability. Their capacity to spontaneously create nanoemulsions within the gastrointestinal (GI) tract is one of their greatest assets to their success. This enhances the surface space on which it can release drugs and hence become readily and most effectively dissolved even in highly lipophilic molecules that are naturally poorly soluble in water [33]. The resulting

nano-sized droplets keep the drug in a supersaturated and dissolved state throughout the GI transit, avoiding the precipitation of the drug, a limitation that is typical with the traditional formulations [34]. SNEDDS also enhance the effective permeability of intestinal epithelia membranes. Membrane fluidity can be temporarily altered in the presence of a certain type of a surfactant like polysorbates, or polyoxyl glycerides, which leads to enhanced paracellular and transcellular transport [35]. Moreover, a number of studies suggest that SNEDDS has the capacity to suppress efflux transporter including P-glycoprotein (P-gp), and thereby, increase absorption of drugs that are subject to efflux-induced bioavailability decrease [36].

Table 5. Key Mechanisms Contributing to SNEDDS Clinical Success

Mechanism	Clinical Benefit
Rapid nanoemulsion formation	Faster dissolution & improved absorption
Precipitation prevention	Consistent bioavailability
Membrane permeability enhancement	Increased drug transport across epithelium
Efflux inhibition (e.g., P-gp)	Higher systemic exposure
Lymphatic uptake	Bypass of first-pass metabolism
Lipolysis-driven micelle formation	Sustained solubilization

The other significant mechanism of clinical success of SNEDDS is that they facilitate lymphatic drug delivery. In this route, the drug does not undergo hepatic first-pass metabolism, and the drug has increased systemic exposure and higher bioavailability when the lipophilic drugs have high log P values [37]. Improved dose proportionality, held by lymphatic uptake, also helps in the low pharmacokinetic variability and other favorable characteristics in clinical trials of immunosuppressive agents and antiviral agents [38]. The enhanced use of SNEDDS is further enhanced by the lipid digestion process. Bile salts and phospholipids interact with the

lipid droplets of nanoemulsions during the lipolysis process and resulting in the formation of mixed micelles and vesicles among other colloidal structures that can dissolve drug molecules and transport them across the intestinal mucosa [39]. These active changes promote a state of sustained supersaturation and effective absorption of drugs. The supersaturable SNEDDS (S-SNEDDS) and solid SNEDDS (S-SNEDDS) have added to the clinical performance through the optimization of formulations stability, decreased excipient load, and increased convenience among patients [40]. A combination of these processes justifies

SNEDDS as a potent platform that can break down the constraints of biopharmaceuticals and provide clinically significant changes in drug treatment.

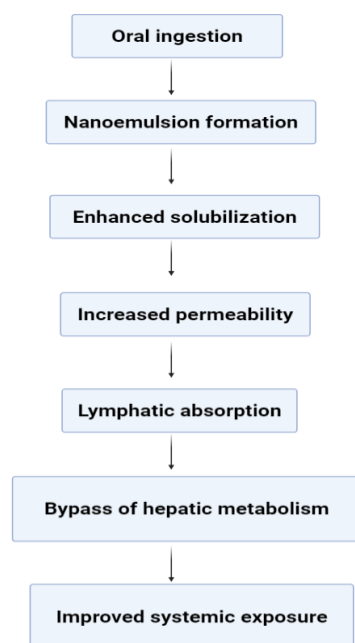


Figure 2. *Mechanistic Pathways Underlying SNEDDS Clinical Performance*

2. SNEDDS: SCIENCE OF FUNDAMENTALS AND FORMULATION

Self-nanoemulsifying drug delivery systems (SNEDDS) are among the new types of lipid-based formulation that aims at improving the solubility, speed of dissolution, and oral bioavailability of water insoluble drugs. They are the self-emulsifying oils, surfactants and co-surfactant isotropic blends that spontaneously form fine oil-in-water nanoemulsions when diluted in the gastrointestinal (GI) fluids with mild agitation, say that of peristalsis [11]. Development of nano-sized droplets (usually 20-200 nm) is a great enhancement to the surface area leading to fast drug release and enhanced absorption across the intestinal membrane. The main principle of SNEDDS efficiency in this area is that they allow keeping the lipophilic drugs in a solvated form during the process of their GI passage. This averts precipitation which is the primary drawback of the

traditional formulations hence affording steadier absorption profiles [12]. Also, the high content of surfactants enhances increased membrane permeability and could also block other efflux transporter like P-glycoprotein (P-gp) and allow improved bioavailability of those drugs which undergo extensive efflux or first-pass metabolism [13]. The SNEDDS formulation development involves about the selection of the use of the relevant excipients according to the solubility studies, efficacy of emulsification, and distribution of droplet sizes as well as thermodynamic stability and conformity to regulatory requirements as well. Oils improve solubilization and lymphatic uptake, surfactants lower interfacial tension, and co-surfactants give the interfacial film flexibility, increasing the stability of nanoemulsion [14].

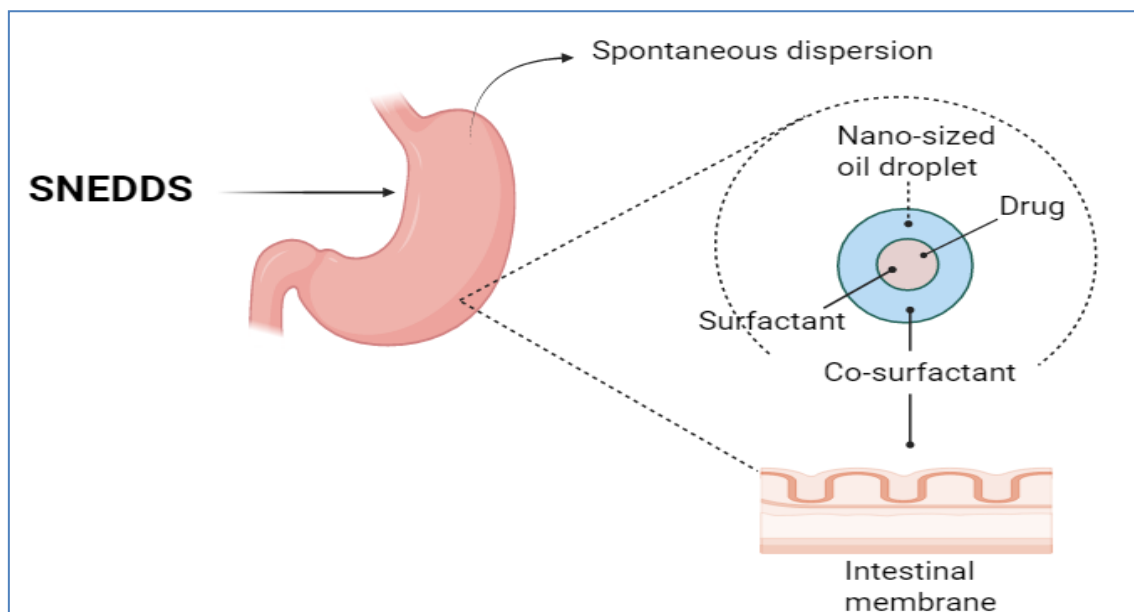


Figure 3. Schematic Representation of SNEDDS Formation Mechanism

According to the latest technological interventions, modified systems, including, but not limited to, supersaturable SNEDDS (S-SNEDDS), in which precipitation inhibitors prevent the formation of crystallized drugs; and solid-SNEDDS (S-SNEDDS), in which liquid formulations become solid dosage forms with drug-nanoemulsifying properties retained have been developed with technology [15]. These technologies overcome major issues of capsule leaking, the instability of the excipients, and low levels of patient acceptability. Typical physicochemical characterization experiments are droplets size analysis, zeta potential determination, cloud-point determination and dilution resolution. An in vitro dispersion testing and model of lipolysis gives predictive information of in vivo behavior, and optimizes formulations before mice testing [16]. In general, SNEDDS still represent a scientifically contingent and industrializable system of overcoming solubility and permeability restrictions in oral drugs delivery.

4. GLOBAL UTILISATION OF SNEDDS IN THE PHARMACEUTICAL INDUSTRY

The self-increasing trend of use of Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) throughout the globe has grown over the past twenty years due to emerging awareness of the potential of such systems to boost the oral absorption of sparingly water-soluble drugs. Emerging markets, like India and Brazil have had SNEDDS platforms incorporated in their developmental pipelines and commercial drug products in European, United States and Japanese pharmaceutical industries [17]. The contribution of the substantial improvement in bioavailability, enhanced therapeutic regularity, and lower inter-individual variability accompanying SNEDDS-based preparations to this global acceptance has gone a long way. A number of commercial products, such as cyclosporine (Neoral(r)), ritonavir (Norvir(r)) and fenofibrate lipid-based SNEDD systems have shown that SNEDDS technology can indeed be effectively applied to transfer laboratory research into clinical and commercial practice [18].

Table2. Commercially available SNEDDSs formulations

Product Name	Drug	Therapeutic Use	BCS Class	Marketed Dosage Form	Company	Patent detail
Gengraf®	Cyclosporine A/III	Immunosuppressant	IV	Hard gelatin capsule	AbbVie Inc.	U.S. Patent No. 5,342,625
Neoral®	Cyclosporine	Immunosuppressant	IV	Soft gelatin capsule	Novartis pharmaceuticals corporation	U.S. Patent No. 5,741,512
Norvir®	Ritonavir	Adjunctive therapy with other antiretroviral agents during HIV-1 infection	II	Soft gelatin capsule	AbbVie Inc.	U.S. Patent No. 5,541,206

REVIEW PAPER

Fortovase®	Saquinavir	HIV infection	IV	Soft gelatin capsule	Roche Laboratories Inc.	U.S. Patent No. 6,008,228
Agenerase®	Amprenavir	HIV infection	II	Soft gelatin capsule	GlaxoSmith Kline	U.S. Patent No. 5,585,397
Aptivus®	Tipranavir	HIV infection	II	Soft gelatin capsule	Boehringer Ingelheim Pharmaceuticals Inc.	U.S. Patent No. 5,852,195(develop primary compound Tipranavir), U.S. Patent No, 6,147,095
Depakene®	Valporic acid	Used in patients with partial seizures	II	Soft gelatin capsule	AbbVie Inc.	US5017613A (valproic acid preparation), US5019398A (sustained-release tablet)
Rocaltrol®	Calcitriol	Hyperparathyroidism and hypocalcemia	II	Soft gelatin capsule	Roche Products Limited	Original Patent expired while specific formulation related patent exist such as CN103784419A for softgel, WO2017118885A 1for stable composition and WO2001022998A 1 for solution.
Targretin®	Bexarotene	Treatment of cutaneous T-cell lymphoma	II	Soft gelatin capsule	Ligand Pharmaceuticals	U.S. Patent No. 5,780,676, U.S. Patent No. 5,962,731 expired in 2015 & 2016 allowing for the entry of generic formulations.
Vesanoid®	Tretinoin	Maturation of acute promyelocytic leukemia (APL)	II	Soft gelatin capsule	Roche Laboratories Inc.	French patent No. 71/22860 (status expired)
Accutane®	Isotretinoin	Recalcitrant nodular acne	II	Soft gelatin capsule	Roche Laboratories Inc.	U.S. Pat. No. 4,464,394 (approved 1983 & status expired)
Rapamune®	Sirolymus	Immunosuppressant and anti-proliferative	II	Soft gelatin capsule	Pfizer	U.S. Patent No. 5,989,591 (Rapamycin formulations for oral administration &

						expired in March 2018)
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Another factor that affects global utilization is the growing number of lipid-based formulation research, as well as the increasing number of the BCS Class II/IV drug candidates. According to Asia-Pacific markets especially India and China, strong SNEDDS development activity is recorded by cost-effective manufacturing, academia-industry partnerships, and generic reformulations with high bioavailability are sought [21]. Also, innovations in technology include the use of SNEDDS (super saturated), solid- SNEDDS, and SNEDDS controlled-release hybrid have increased the industrial application of next-generation formulations [22]. Although it has generated much interest, factors like the variability in excipient, scalability of manufactures and lack of harmonisation of regulatory

expectations have been some of the issues that affect global adoption. However, the growing number of patents, clinical testing and marketed formula is solid testimony to the growing global presence of SNEDDS [23]. There is also a trend that multinational companies are using SNEDDS to increase the life cycle of product, increase therapeutic index and improve performance of previously poor molecules [24]. On the whole, the world use of SNEDDS indicates the transition into the technology of sophisticated lipid-based oral drug delivery. The further adoption of SNEDDS in the next decades is likely to be boosted by additional innovation, harmonisation of regulatory frameworks, as well as successful stories of commercial success achieved by its use [25].

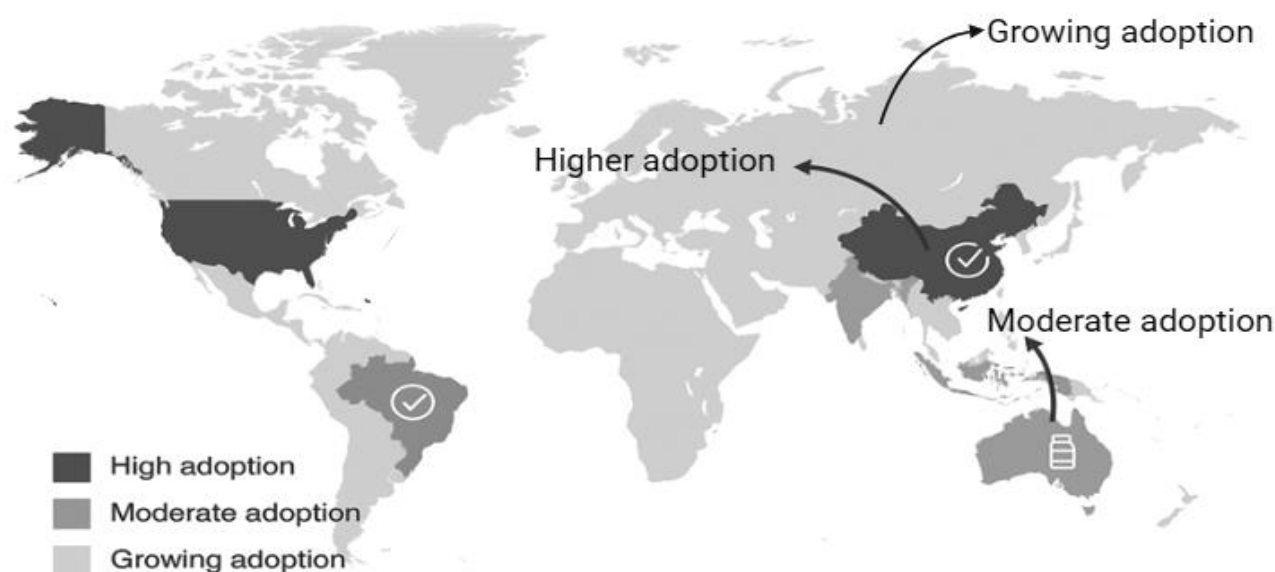


Figure 4. Global Distribution of SNEDDS Utilization

5. CLINICAL SIGNIFICANCE OF SNEDDS: EVIDENCE FROM TRIALS

Self-Nanoemulsifying Drug Delivery System (SNEDDS) has been strongly supported by clinical evidence of the world trials to improve the therapeutic effect of insoluble drugs in water. The pharmacokinetic (PK)-clinical experiments conducted have found a considerable enhancement of drug absorption, systemic exposure, and therapeutic outcome consistency during the utilization of SNEDDS formulation instead of the traditional oral dosage forms. Among the best-known ones there is cyclosporine, in which reformulation as a SNEDDS resulted in a significant decreasing effect on inter-individual variability and led to a significant increase in bioavailability, dramatically improving therapeutic control in transplant patients [26]. Also, a clinical trial of ritonavir and lopinavir SNEDDS versions showed superior solubility, which results in

superior antiviral results and decreases dose demands [27]. An additional lipid-modified drug, fenofibrate, showed an SNEDDS-enhanced bioavailability over micronized delivery systems almost 200-fold in promoting more predictable lipid-lowering in dyslipidemic patients [28]. SNEDDS achieve not only improved PK parameters including C_{max} and AUC but also help to achieve reductions in food-dependent variability which is a frequent problem with lipophilic drugs. A number of clinical trials have demonstrated that SNEDDS continue to remain bioavailable in a fed and fasted state, enhancing treatment congruence and patient adherence [29]. In addition, the ability of SNEDDS to evade first-pass metabolism by lymphatic uptake has already been established using human models in the context of highly lipophilic molecules, which enables more stable plasma concentration and less dose-dependent toxicity [30].

Table 4. *Selected Clinical Trials Demonstrating SNEDDS Efficacy*

Drug	Clinical Outcome	Key Improvement
Cyclosporine	Reduced variability	↑ Bioavailability & consistent absorption
Ritonavir	Enhanced antiviral response	↑ Solubility & PK exposure
Fenofibrate	Better lipid control	↑ AUC & Cmax vs. micronized forms
Antihypertensives	Rapid onset	Faster nanoemulsion formation

In addition to their effect on bioavailability the SNEDDS have proven useful in therapeutical response. As an example, SNEDDS-based antihypertensive and antidiabetic drug formulations showed quicker activation of activity and better symptoms control in Phase II research owing to rapid nanoemulsions creation in the gastrointestinal tract [31]. Also, oncology studies of SNEDDS-loaded chemotherapeutics showed better tolerability and decreased gastrointestinal side effects mostly because of controlled solubilization and decreased precipitation in vivo [32].

With the increasing body of clinical evidence, SNEDDS are being considered beyond a solubility enhancer and now have become effective, and valid clinically as a means of maximizing drug therapy. Their performance through use of increased absorption, reduced variability, and improved patient outcomes highlight their growing clinical practice/pharmacological development value.

10. CONCLUSION

The global adoption of Self-Nanoemulsifying Drug Delivery System (SNEDDS) is indicative of a paradigm shift in the pharmaceutical world toward improved lipid-based technology that can cross the obstacles related to therapeutic agents that are not very soluble in water. The underlying principles of improved solubilization, increased permeability, inhibition of efflux and lymphatic uptake have been proven in a large number of clinical trials and make SNEDDS a powerful and dependable formulation platform. The results of this review demonstrate that SNEDDS have consistent bioavailability, pharmacokinetic stability, and therapeutic performance with a wide range of classes of drugs, including immunosuppressive and antiviral, cardiovascular drugs, and cancer therapeutic agents. Worldwide evidence indicates that SNEDDS have revolutionized the clinical performance of a range of lipophilic drugs that in the past experienced handling issues associated with low solubility and wide interpersonal variability. The improved absorptive characteristics exhibited by the SNEDDS-based drugs are attributed to the characteristics of maintaining supersaturation and avoidance of precipitation upon exposure to the gastrointestinal environment, thus guaranteeing reliable therapy exposure. Such benefits become better patient compliance, decreased dose frequency, and predictable responses, particularly in

classes of therapeutics with narrow therapeutic indices, including transplantation drugs and antiretroviral therapy.

Another technological improvement that has enhanced the clinical viability of SNEDDS is also noted in the review. Solid-state SNEDDS and the supersaturable (S-SNEDDS) have also previously overcome limitations based on chemical instability, capsule leakages, and excipient compatibility issues among other factors. These innovations have made scale up and commercialization quite easy due to enhanced stability, handling ease, and manufacturability, necessary to embrace the global market role.

The Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) have become a paradigm shift in the delivery of oral drugs with clinically proven solutions to the barriers that have been in place concerning the poor solubility of therapeutics in water. SNEDDS have the ability to improve drug absorption and therapeutic consistency by improving solubilization, membrane permeability, reducing efflux and allowing lymphatic uptake to counter the barriers of the conventional formulations and provide the biggest percentage of drug absorption and consistency. The versatility of SNEDDS and its wide applicability in therapeutics is evidenced by the usage of SNEDDS in a wide spectrum of therapeutic classes, such as immunosuppressant, antivirals, cardiovascular agents, oncolytic agents, CNS therapeutics, and phytochemicals, worldwide. Their stability, patient's acceptability and regulatory compliance have been further improved by technological advancements including supersaturable SNEDDS (S-SNEDDS), solid-SNEDDS (S-SNEDDS), and hybrid lipid-based nanoformulations which have assisted in ensuring the successful translation of laboratory development into commercial pharmaceutical products. Even with the demonstrated advantages, safety optimization, excipient toxicity, stability over time and the harmonization of international regulatory frameworks are still problematic. These gaps will be critical towards the expansion of SNEDDS applications as well as ensures of reliable and patient friendly formulations.

In general, SNEDDS are a great alternative of bioavailability and therapeutic efficacy enhancement that is adopted worldwide, especially

to address the bioavailability and bio-membrane deficiencies of drugs with weak solubility or permeability. As further developments are made on formulation science, predictive modeling and composition of regulations, SNEDDS will continue being on the leading edge of the novel oral system of drug delivery, facilitating more efficient, secure and accessible treatment all over the world.

References

1. Ujilestari T, Martien R, Ariyadi B, Dono ND. Self-nanoemulsifying drug delivery system (SNEDDS) of Amomum compactum essential oil: design, formulation, and characterization. *J. Appl. Pharm. Sci.* 2018; 8:14–21.
2. Pouton, C.W. Formulation of Self-Emulsifying Drug Delivery Systems. *Adv. Drug Deliv. Rev.* 1997, 25, 47–58.
3. Pouton, C.W. Lipid Formulations for Oral Administration of Drugs: Non-Emulsifying, Self-Emulsifying and ‘Self Microemulsifying’ Drug Delivery Systems. *Eur. J. Pharm. Sci.* 2000, 11, S93–S98.
4. Gershanik, T.; Benita, S. Self-Dispersing Lipid Formulations for Improving Oral Absorption of Lipophilic Drugs. *Eur. J. Pharm. Biopharm.* 2000, 50, 179–188.
5. Amidon, G.L.; Lennernäs, H.; Shah, V.P.; Crison, J.R. A Theoretical Basis for a Biopharmaceutical Drug Classification: The Correlation of in Vitro Drug Product Dissolution and In Vivo Bioavailability. *Pharm. Res.* 1995, 12, 413–420.
6. Cerpnjak, K.; Zvonar, A.; Gašperlin, M.; Vrecer, F. Lipid-Based Systems as a Promising Approach for Enhancing the Bioavailability of Poorly Water-Soluble Drugs. *Acta Pharm.* 2013, 63, 427–445.
7. Abubakr Soliman, K.; Kamal Ibrahim, H.; Mohamed Ghorab, M. Formulation of Risperidone as Self-Nanoemulsifying Drug Delivery System in Form of Effervescent Tablets. *J. Dispers. Sci. Technol.* 2012, 33, 1127–1133.
8. Zhu, Y.; Ye, J.; Zhang, Q. Self-Emulsifying Drug Delivery System Improve Oral Bioavailability: Role of Excipients and PhysicoChemical Characterization. *Pharm. Nanotechnol.* 2020, 8, 4.
9. Gao, P.; Jiang, Z.; Luo, Q.; Mu, C.; Cui, M.; Yang, X. Preparation and Evaluation of Self-Emulsifying Drug Delivery System (SEDDS) of Cepharranthine. *AAPS Pharm Sci Tech* 2021, 22, 245.
10. Cherniakov, I.; Domb, A.J.; Hoffman, A. Self-Nano-Emulsifying Drug Delivery Systems: An Update of the Biopharmaceutical Aspects. *Expert. Opin. Drug Deliv.* 2015, 12, 1121–1133.
11. Nanjwade, B.K.; Patel, D.J.; Udhani, R.A.; Manvi, F.V. Functions of Lipids for Enhancement of Oral Bioavailability of Poorly Water-Soluble Drugs. *Sci. Pharm.* 2011, 79, 705–728.
12. Salawi, A. Self-Emulsifying Drug Delivery Systems: A Novel Approach to Deliver Drugs. *Drug Deliv.* 2022, 29, 1811–1823.
13. Singh, S.; Bajpai, M.; Mishra, P. Self-Emulsifying Drug Delivery System (SEDDS): An Emerging Dosage Form to Improve the Bioavailability of Poorly Absorbed Drugs. *Crit. Rev. Ther. Drug Carr. Syst.* 2020, 37, 305–329.
14. Rajesh, S.Y.; Singh, S.K.; Pandey, N.K.; Sharma, P.; Bawa, P.; Kumar, B.; Gulati, M.; Jain, S.K.; Gowthamarajan, K.; Singh, S. Impact of Various Solid Carriers and Spray Drying on Pre/Post Compression Properties of Solid SNEDDS Loaded with Glimepiride: In Vitro-Ex Vivo Evaluation and Cytotoxicity Assessment. *Drug Dev. Ind. Pharm.* 2018, 44, 1056–1069.
15. Kuncahyo, I.; Choiri, S.; Fudholi, A. Solidification of Meloxicam Self-Nano Emulsifying Drug Delivery System Formulation Incorporated into Soluble and Insoluble Carriers Using Freeze Drying Method. *IOP Conf. Ser. Mater. Sci. Eng.* 2019, 578, 012051.
16. Gade, M.M.; Hurkadale, P.J. Formulation and Evaluation of Self-Emulsifying Orlistat Tablet to Enhance Drug Release and in Vivo Performance: Factorial Design Approach. *Drug Deliv. Transl. Res.* 2016, 6, 276–288.
17. Czajkowska-Kośnik, A.; Szekalska, M.; Amelian, A.; Szymańska, E.; Winnicka, K. Development and Evaluation of Liquid and Solid Self-Emulsifying Drug Delivery Systems for Atorvastatin. *Molecules* 2015, 20, 21010–21022.
18. Sharma S, Bajaj H, Bhardwaj P, Sharma AD, Singh R. Development and characterization of self emulsifying drug delivery system of a poorly water soluble drug using natural oil. *Acta Pol Pharm Drug Res.* 2012; 69(4):713–7.
19. Chintalapudi R, Murthy TEGK, Lakshmi KR, Manohar GG. Formulation, optimization, and evaluation of self-emulsifying drug delivery systems of nevirapine. *Int J Pharm Investig.* 2015; 5(4):205–13.
20. . Agency Em. EMA - Norvir authorization 1996. EMA; 2015 [cited 2024 Nov 19]. Available from:

- <https://www.ema.europa.eu/en/medicines/human/EPAR/norvir>.
21. Zafar A, Imam SS, Alruwaili NK, et al. Development of piperineloaded solid self-nanoemulsifying drug delivery system: optimization, in-vitro, ex-vivo, and in-vivo evaluation. *Nanomaterials*. 2021, 11:2920.
22. Akiladevi D, Prakash H, Biju G, Madumitha N. Nanonovel approach: self nano emulsifying drug delivery system (SNEDDS)-review article. *Res J Pharm Technol*. 2020, 13:983.
23. Farooqui H, Upadhyay S, Upadhyay P. Transdermal patches approach towards self-nano-emulsifying drug delivery system (SNEDDS) using essential oil as penetration enhancer. *Micro Nano syst*. 2022, 14:314–40.
24. Khan AW, Kotta S, Ansari SH, Sharma RK, Ali J. Self-nanoemulsifying drug delivery system (SNEDDS) of the poorly watersoluble grapefruit flavonoid Naringenin: design, characterization, in vitro and in vivo evaluation. *Drug Deliv*. 2015, 22:552–61.
25. Sumirtapura YC, Pamudji JS, Mudhakir D, Suhery WN. Development and characterization of self-nanoemulsifying drug delivery system (SNEDDS) formulation for enhancing dissolution of fenofbric acid. *J Res Pharm*. 2020;24:738–47
26. Annisa R, Mutiah R, Yuwono M, Hendradi E. Nanotechnology approach-self nanoemulsifying drug delivery system (SNEDDS). *Int J Appl Pharm*. 2023; 12–19.
27. Bandivadekar M, Pancholi S, Kaul-Ghanekar R, Choudhari A, Koppikar S. Single non-ionic surfactant based self-nanoemulsifying drug delivery systems: formulation, characterization, cytotoxicity and permeability enhancement study. *Drug Dev Ind Pharm*. 2013, 39:696–703.
28. Uttreja P, Karnik I, Adel Ali Youssef A, Narala N, et al. Self-emulsifying drug delivery systems (SEDDS): transition from liquid to solid—a comprehensive review of formulation, characterization, applications, and future trends. *Pharmaceutics*. 2025, 17:63.
29. Kim JS, Din Fud, Cho HJ, et al. Impact of carrier hydrophilicity on solid self nano-emulsifying drug delivery system and self nano-emulsifying granule system. *Int J Pharm*. 2023, 648:123578.
30. Shahba AA-W, Mohsin K, Alanazi FK, Abdel-Rahman SI. Optimization of self-nanoemulsifying formulations for weakly basic lipophilic drugs: role of acidification and experimental design. *Braz J Pharm Sci*. 2016, 52:653–67.
31. Mohd AB, Sanka K, Bandi S, Diwan PV, Shastri N. Solid self-nanoemulsifying drug delivery system (S-SNEDDS) for oral delivery of glimepiride: development and antidiabetic activity in albino rabbits. *Drug Deliv*. 2015, 22:499–508.
32. Chen ML. Lipid excipients and delivery systems for pharmaceutical development: a regulatory perspective. *Adv Drug Deliv Rev*. 2008, 60(6): 768-777.
33. Gursoy RN, Benita S. self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drug. *Biomed Pharmacother*. 2004, 58(3):173-182.
34. Humberstone AJ, Charman WN. Lipid-based vehicles for the oral delivery of poorly water soluble drugs. *Adv Drug Deliv Rev*. 1997, 25(1):103-128.
35. Porter CJH, Pouton CW, Cuine JF, Charman WN. Enhancing intestinal drug solubilization using lipid-based delivery systems. *Adv Drug Deliv Rev*. 2008, 60(6):673-691.
36. Rahman MA, Harwansh R, Mirza MA, Hussain S, Hussain A. Oral lipid based drug delivery system (LBDDS): Formulation, characterization and application: a review . *Curr Drug Deliv*. 2011, 8(4):330-345.
37. Laffleur, F.; Millotti, G.; Lagast, J. An overview of oral bioavailability enhancement through self-emulsifying drug delivery systems. *Expert Opin. Drug Deliv*. 2025, 22, 659–671.
38. . Rajeshwar V, Shrivastava B. Self emulsifying drug delivery system (SEDDS): a conventional and alternative approach to improve oral bioavailability. *Int J Pharm Sci Res*. 2018, 9(8):3114–3114.