JURNAL ILMU KEFARMASIAN INDONESIA
Indonesian Journal of Pharmaceutical Sciences
ISSN p-ISSN 1693-1831 (Print) e-ISSN 2614-6495 (Online) PUBLISHER : Faculty of Pharmacy Universitas Pancasila

Impact of SNEDDS formulation variables on physical characterization, drug release, and anti-inflammatory activity: a review

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Received: 28 January 2026 / Accepted: 30 April 2026

ABSTRACT: Self-nano-emulsifying drug delivery systems (SNEDDS) address the challenges of poor solubility and bioavailability in oral drug delivery. These challenges lead to poor therapeutic results and an increased frequency of dosing. This review assesses the challenges of oral drug delivery due to poor solubility and absorption and the potential of Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) to deliver poorly water-soluble drugs. This also entails an assessment of the formulation components of SNEDDS, particularly oils, surfactants, and co-surfactants, and their influence on the physicochemical properties, release profile, stability, and anti-inflammatory activity of the formulation. A thorough assessment of 25 of the most recent primary studies revealed the significant influence of formulation design on the size and distribution of droplets and their subsequent emulsification, drug release, and bioavailability. Oils that are easier to solubilize, along with high HLB surfactants and co-surfactants, such as PEG 400 and Transcutol, are instrumental in producing smaller, stable emulsions that facilitate permeability. Nevertheless, human pharmacokinetic data are lacking, and challenges remain in the large-scale production of solid dosage forms from liquid SNEDDS. This problem is further complicated by the variability of the excipients. The review highlights the need for standardized predictive models and more refined plans for in vivo validation and excipient development. What is unique is the integration of specific information from formulation optimization with translational pharmacological outcomes. This integration has the potential to greatly improve the design and utilization of SNEDDS, thereby expanding its therapeutic benefits.

KEYWORDS: Anti-inflammatory; characterization; drug release; review; SNEDDS.

▪ INTRODUCTION

Compromised therapeutic outcomes have been a problem in oral drug delivery over the last decade because of the inconsistent solubility and availability of bioactive pharmaceutical components (APIs). This problem is exacerbated by the requirement for frequent dosing and high drug doses. Hot-melted drug delivery systems (SNEDDS) are an inventive approach to improve the solubility of poorly soluble drugs. Their potential to improve the absorption of suboptimally water-soluble drugs makes them unique. Their synthesis requires low manufacturing and thermodynamic stability, and the nano-emulsions formed after interaction with in vivo gastrointestinal (GI) fluids are smaller in droplet size and uniformly dispersed. Recent research has shown that the use of SNEDDS improves the reliability of drug delivery and enhances drug release, storage stability, and drug bioavailability in vivo, especially in the treatment of almost all injurious conditions [1],[2].

Most review research assesses the correlation between the physical characteristics and emulsions and the composition of various nano-emulsions. Few studies have analyzed the impact of structured emulsions, fluids, and surfactants, as well as the systemic stability, drug release, and anti-injury effects of selected nanoemulsions. The SNEDDS emulsions used contain oils that act as important solubilizing matrices, thereby affecting the emulsions and API stability primarily with the solubility. Surfactants with a greater hydrophilic-lipophilic balance (HLB) are key to rapid self-emulsification, smaller droplet sizes, higher drug loading capacity, and interfacial tension-lowering co-surfactants such as PEG 400 or Transcutol, for system

How to cite this article: Ulfa R, Iskanda B, Novita G, Anggraini D, Suhery WN, Putra PA. Impact of SNEDDS formulation variables on physical characterization, drug release, and anti-inflammatory activity: a review. Jurnal Ilmu Kefarmasian Indonesia. 2026. 24(1): 161-173.

https://doi.org/10.35814/jifi.v24i1.2050
ISSN: 2614-6495

stabilization and improved bioavailability. The ideal ratio and nature of these constituents determine the droplet size, polydispersity index, and zeta potential of the nanoemulsions, and consequently the effective drug release, stability, and anti-inflammatory response, sustained for an extended duration by oral or topical delivery [3].

Significant advancements have been made in the rational design and mechanistic understanding of SNEDDS-based formulations. However, gaps in knowledge still remain. Traditional methods of improving solubility, such as salt formation, micronization, and the use of solid dispersions, have been shown to be ineffective in overcoming the multiple challenges of drug absorption and stability in the GI tract. In contrast, SNEDDS has the unique advantages of spontaneous emulsification and absorption through the lymphatic system. However, the selection of excipients and their compatibility with a wide range of active pharmaceutical ingredients remain unclear. Previous reviews have largely concentrated on either drug formulation science or particular classes of drugs, without demonstrating the correlation between formulation and numerous in vitro and in vivo parameters such as drug release, stability, and anti-inflammatory actions. This has resulted in increasing gaps in SNEDDS systems in relation to traditional systems, mechanisms of overcoming absorption barriers, and bioavailability and tissue distribution. An additional focus on safety, in the context of a holistic mechanistic approach, is the most pressing need in this area [1].

This review aims to evaluate and summarize the recent literature from 2016-2026 and analyze the impact of formulation variables of SNEDDS on the physical properties, pharmacokinetics, and pharmacodynamics of SNEDDS, particularly in inflammation-initiated diseases. The analysis includes various experimental studies on oils, surfactants, and co-surfactants and their relationships with particle size and stability, drug release and bioactivity, and overall biological performance. The synthesis of this review will assist in the formulation of SNEDDS in a more precise and up-to-date manner, highlight the advantages of SNEDDS over other methods, and address the gaps, challenges, and prospects of SNEDDS as a delivery system for medications.

▪ MATERIALS AND METHODS

In line with the PRISMA protocol for systematic reviews, studies on Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) were systematically searched. The search strategy was designed using keywords and Boolean Operators (e.g., "AND," "OR") to ensure comprehensive coverage of the problem area. The principal search string contained: ("SNEDDS" OR "Self-Nanoemulsifying Drug Delivery Systems) AND ("formulation" OR "formulation variables") AND ("characterization" OR "physical properties") AND ("drug release" OR dissolution) AND ("anti-inflammatory" OR antiinflammatory).

To obtain peer-reviewed or frequently indexed scientific publications, a literature search was conducted using electronic databases such as PubMed, Scopus, Semantic Scholar, and Google Scholar. We limited our search to articles published in English and Indonesian and placed restrictions on the publication year (2016-2026). Additional studies were identified through manual searches of the reference lists of the included studies. In the identification phase, all records retrieved from the databases were exported. All records were organized using reference management software. Before screening, duplicate records were removed. To detect study relevance, titles and abstracts were screened against the eligibility criteria. Studies dealing with SNEDDS formulation, physicochemical characterization, drug release behavior, and anti-inflammatory activity were included for full-text evaluation. At this stage, any studies that were not SNEDDS-related, experimental, or review, or not related to any key variables of interest were discarded.

During the eligibility phase, full-text articles of studies deemed potentially eligible were retrieved and assessed in detail. Only articles that provided detailed information on how formulation variables affect the performance of SNEDDS, along with physical characterization, dissolution or drug release profiles, and anti-inflammatory evaluation were selected. We excluded studies with insufficient data, non-scientific reports, and irrelevant outcomes. Ultimately, studies that satisfied all the inclusion criteria were included in the qualitative synthesis. The selection process was documented using a PRISMA flow diagram detailing the number of records identified, screened, excluded, and included at each stage. The literature selection process was systematic, making the document consistent, reproducible, and rigorous. The PRISMA flow diagram is shown in Figure 1.

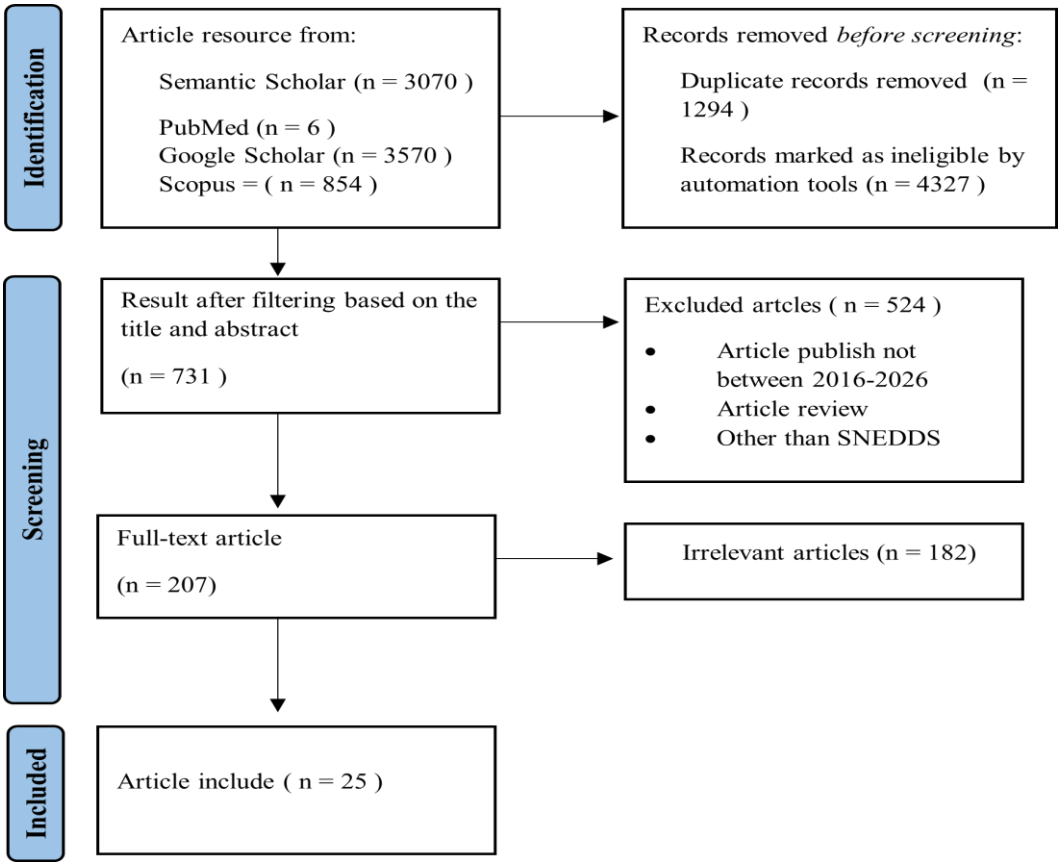

Figure 1. PRISMA flow diagram of the literature search.

RESULTS

From the literature search using various databases, 25 articles were identified that investigated the influence of SNEDDS formulations on physical characterization, drug release, stability, and anti-inflammatory activity. The SNEDDS formulations consisted of oil, surfactants, and co-surfactants. Each study employed different active compounds, oils, surfactants, and co-surfactants, and their effects on physical characterization, stability, drug release, and anti-inflammatory activity are summarized in Tables 1 and 2.

Table 1. Formulation, characterization, and stability of SNEDDS.

Active ingredient	Formula	Characteristics	Stability	References
Black cumin oil and olive oil	Oil: Black cumin oil and olive oil Surfactant: Cremophor RH 40 Co-surfactant: PEG 400	Transmittance percentage: 97.27% Particle size: 46 nm Emulsification time: <60 seconds (Grade A)	Thermodynamic stability test Centrifugation: Stable Heating-cooling cycle: Stable Freeze-thaw cycle: Stable	[4]
White turmeric rhizome oil	Oil: Miglyol Surfactant: Tween 80 Co-surfactant:	Transmittance percentage: 84.47±1.05% Particle size: 15.75 nm Zeta potential: -8.54 mV	Thermodynamic stability test Heating-cooling cycle: Stable Freeze-thaw cycle: Stable	[5]

Active ingredient	Formula	Characteristics	Stability	References
	PEG 400	PDI: 0.188 Emulsification time: 49.67±1.7 seconds (Grade A)		
Mahogany seed oil	Oil: Oleic acid Surfactant: Cremophor RH 40 Co-surfactant: PEG 400	Transmittance percentage is calculated as follows: 99.3%±0.4359 Particle size: 17.7±0.3 nm Zeta potential: -22.67±0.4726 mV Emulsification time: 74.04±6.0542 seconds	-	[6]
Ibuprofen	Oil: Propylene glycol monocaprylate Surfactant: Polysorbate 20 Co-surfactant: PEG 400	Transmittance percentage is calculated as follows: 99.98±0.01% Particle size: 12.63±1.68 nm Zeta potential: -24.37±0.29 mV	Thermodynamic stability test Centrifugation: Stable Heating-cooling cycle: Stable Freeze-thaw cycle: Stable Accelerated stability study: SNEDDS preparations remain stable when stored at a temperature of (40±2°C/RH 75±5%) for 1 month	[7]
Pineapple peel	Oil: Virgin coconut oil (VCO) Surfactant: Tween 80 Co-surfactant: PEG 400	Percent trans fat: 98.6% Particle size: 15.06 nm Zeta potential: -14.3 mV Emulsification time: 24.93 seconds (Grade A)	Nanoemulsion stability test: The formed nanoemulsion is stable in distilled water medium	[8]
Mefenamic acid	Oil: Virgin coconut oil (VCO) Surfactant: Tween 80 and Span 80 Co-surfactant: PEG 400	Percent transmittance: 89.04% Particle size: 153.5 nm Zeta potential: 8.2 mV Emulsification time: <60 seconds (Grade A)	Nanoemulsion stability test: The nanoemulsion formed remained stable in distilled water for 4 hours of observation	[9]
Papaya leaf extract	Oil: Isopropyl myristate Surfactant: PEG 400 Cosurfactant:	Percentage transmittance: 94.492% Particle size: 77.1 nm PDI: 0.416	Thermodynamic stability test Freeze-thaw cycle: Stable	[10]

Active ingredient	Formula	Characteristics	Stability	References
	Tween 80			
Karamunting leaf extract	Oil: Capryol 90 Surfactant: Tween 20 and Tween 80 Co-surfactant: PEG 400	Percentage transmittance: 97.50±0.0023 % Particle size: 11.33±2.06 nm Zeta potential: -39.57±0.68 mV PDI: 0.42±0.24	-	[11]
Astaxanthin	Oil: Oleic acid Surfactant: Tween 20 Co-surfactant: Propylene glycol	Transmittance percentage is calculated as follows: 95 Particle size: 105.75 nm PDI: 0.392 Emulsification time: 37 seconds (Grade A)	Thermodynamic stability test Freeze-thaw cycle: Stable	[12]
Black cumin extract	Oil: Crocodile shark oil Surfactant: Tween 80 Co-surfactant: PEG 400	Percent transmittance: 98.37% Particle size: 16.3 nm PDI: 0.202 Zeta potential: -43.5 mV Emulsification time: 47.35 seconds	Thermodynamic stability test Freeze-thaw cycle: Stable	[13]
Ethyl p-methoxycinnamate (EPMS)	Oil: VCO Surfactant: Cremophor RH 40 Co-surfactant: Propylene glycol	Percent transmittance: 95.43% Particle size: 30.16 nm PDI: 0.160 Zeta potential: -61.03 mV Emulsification time: 8.33 minutes	Thermodynamic stability test Freeze-thaw cycle: Stable	[14]
Capra hircus extract and melon oil	Oil: Goat fat and melon oil Surfactant: Tween 65 and Tween 80 Co-surfactant: Span 85	Particle size: 195 nm PDI: 0.25 Emulsification time: <60 seconds (Grade A)	-	[15]
Papaya leaf extract	Oil: VCO Surfactant: Tween 80 Co-surfactant:	Percent transmittance: 90.77±0.15% Emulsification time: 7.77±0.39 seconds (Grade A)	Thermodynamic stability test Freeze-thaw cycle: Stable	[16]

Active ingredient	Formula	Characteristics	Stability	References
	PEG 400			
Red fruit oil	Oil: Red fruit oil Surfactant: Tween 80 Co-surfactant: Propylene glycol	Transmittance percentage is calculated as follows: 99.34% Emulsification time: 15.40 seconds (Grade A)	-	[17]
Mefenamic acid	Oil: Olive oil Surfactant: Tween 80 Co-surfactant: PEG 400	Percent transmittance: 95 Particle size: 16.8 nm Zeta potential: +2.9 mV Emulsification time: 50 seconds	Thermodynamic stability test Sedimentation: Stable	[18]
Ramania seed extract	Oil: Oleic acid Surfactant: Tween 20 Co-surfactant: Propylene glycol	Percent transmittance: 94.2% Particle size: 161.1 nm PDI: 0.364 Emulsification time: 15.2 seconds	-	[19]
Timokuinon	Oil: Labrafil M2125 Surfactant: Tween 80 Co-surfactant: Plurol oleic	Percent transmittance: 97.6±0.13% Particle size: 90±2.65 nm Zeta potential: −11.35 Mv	Thermodynamic stability test Centrifugation: Stable Heating-cooling cycle: Stable Freeze-thaw cycle: Stable	[20]
Ibuprofen	Oil: Sesame oil Surfactant: Cremophor EL Co-surfactant: PEG 400	Percent transmittance: 94.2% Particle size: 161.1 nm PDI: 0.364 Emulsification time: 15.2 seconds	Stability test: The SNEDDS formulation remained stable after being stored for 6 weeks at temperatures of (27–30 ± 2°C) and (45 ± 2°C)	[21]
Naringenin	**Oil:** Triacetine **Surfactant:** Tween 80 **Co-surfactant:** Transcutol P	Percentage transmittance: 88.74±2.27% Particle size: 14.8 nm Emulsification time: 18.58 ± 0.62 seconds	-	[22]

Table 2. Drug release and anti-inflammatory activity of the SNEDDS formulations.

Active ingredients	Formula	In vitro drug release	Pharmacological activity	References
Curcumin	Oil: Eucalyptus oil Surfactant: Tween 80 Co-surfactant: Transcutol HP	The release profile of curcumin from the SNEDDS preparation followed a biphasic pattern, with an initial burst release (26.33±2.16% in 1.0 h) followed by sustained release up to 78.49%.	Histopathological testing revealed no inflammation in mice administered topical SNEDDS Curcumin. The use of SNEDDS Curcumin on the skin resulted in better wound healing activity than that with pure eucalyptus oil.	[23]
Curcumin	Oil: Miglyol 812 Surfactant: Imwitor 742 Co-surfactant: Cremophor RH40	The highest drug release was observed in SNEDDS F6 (45 mg/g). This was close to the release of the comparator (sodium diclofenac).	In vivo testing revealed that SNEDDS F6 exhibited high anti-inflammatory activity, reducing edema by up to 80% compared to the positive control.	[24]
Single Garlic Extract	Oil: Canola oil Surfactant: Tween 80 Co-surfactant: PEG 400	The release percentages of allicin and aliin from the SNEDDS preparation were 89.34% and 89.31%, respectively, which were higher than those of allicin and aliin that were not formulated in the SNEDDS preparation.	The anti-inflammatory effect of the single onion extract SNEDDS was evaluated based on its potential to reduce pro-inflammatory cytokine production in Methylglyoxal-induced TIG-1 cells using the ICC method. IL-1ß expression in MG-induced TIG-1 cells showed that single onion extract SNEDDS reduced the expression of pro-inflammatory cytokines compared to the control group ($p<0.05$).	[25]
Piroxicam	Oil: Oleic acid Surfactant: Tween 80 Cosurfactant: Propylene glycol	-	The SNEDDS piroxicam formulation exhibited the greatest anti-inflammatory effect compared to the positive control, piroxicam suspension ($p<0.05$). This indicates that mice administered the SNEDDS formulation had lower levels of edema or inflammation than those in the other groups.	[26]
Diacerein	Oil: Diacerein Surfactant: Gelucire 44/14 (Glc) Co-surfactant: d-α-tocopheryl polyethylene	The SNEDDS Diacerein formula significantly increased drug release compared to pure diacerein ($p<0.05$).	The SNEDDS Diacerein formulation significantly ($p<0.05$) reduced edema and inflammation and decreased TNF-α and caspase-3 expression compared to the positive control ( ) and other groups.	[1]

Active ingredients	Formula	In vitro drug release	Pharmacological activity	References
	glycol 1000 succinate (TPGS)			
Cinnamaldehyde	Oil: Coconut oil Surfactant: Tween 80 Co-surfactant: DMSO	-	The SNEDDS formulation of cinnamaldehyde showed a significant reduction in inflammatory markers (NAP) compared to that in the negative control ($p<0.05$).	[27]
Single garlic	Oil: Canola oil Surfactant: Tween 80 Co-surfactant: PEG 400	-	Anti-inflammatory testing of single garlic SNEDDS preparations against the expression of TNF- , and IL-1β affecting 3T3-L1 cells. SNEDDS preparations have the potential to reduce the expression of TNF- , and IL-1β, thereby having an anti-inflammatory effect.	[28]

DISCUSSION

SNEDDS typically consist of an oil, surfactant, and co-surfactant, with formulations tailored to optimize the solubilization, stability, and pharmacological activity of diverse drug candidates, including anti-inflammatory agents. The choice and proportion of these excipients are crucial in determining the physical characteristics, drug release kinetics, stability, and biological performance of the resulting nanoemulsion systems [2],[29].

Recent studies have shown that oil selection is critical for determining the capacity for drug loading and stability of emulsions. Particle size, emulsification time, and spontaneity can be influenced by the surfactant and co-surfactant. Nonionic surfactants, such as Tween 80 and Cremophor, which have high HLB values, are preferred for enhancing dissolution rates as they improve the dispersion of the solution and reduce the size of the droplets. To improve the stability of droplet formation, the tension at the interface is reduced using focosurfactants such as PEG 400 and Transcutol P are used. Finally, thermodynamic stability is regularly obtained by performing stress testing, such as centrifugation, heating and cooling, and freeze-thaw cycles [2-3],[30].

Testing for thermodynamic stability is an important method for evaluating SNEDDS formulations. The stability of the nanoemulsion system was tested under various stresses. Centrifugation testing is a well-known method that simulates long-term gravitational stress by applying a high centrifugal force that accelerates creaming or sedimentation. A physically stable SNEDDS should remain monophasic and show no signs of separation after centrifugation, indicating that a strong interfacial film is formed and droplets are stabilized. Past research has shown that surfactant-cosurfactant-containing formulations are highly resistant to centrifugal stress as a result of lowered interfacial tension and increased kinetic stability [30],[31].

The heating–cooling cycle test further identifies the thermal resistance of the formulation to heat and cold stress. This process simulates actual storage conditions to determine whether temperature fluctuations cause instability, including coalescence or phase inversion. This implies that a stable formulation of a Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) with suitable lipids or surfactants will not undergo any phase separation or precipitation by the product [30],[32]. Together, centrifugation, heating-cooling, and freeze-thaw cycle stress tests are important indicators of the thermodynamic stability of the SNEDDS formulation. The continued successful outcomes of these tests confirm the dependability of the system in sustaining nanoscale characteristics, which is vital for repeatability, a long shelf life, and steady drug release.

This stability ultimately enhances the bioavailability and anti-inflammatory efficacy of the encapsulated drug, as noted in various studies analyzed in this review [2],[30].

Most studies identified sesame oil, oleic acid, VCO, and Miglyol as oils with high solubilization capacities, with reports of better drug release kinetics, increased transmittance, and smaller particle sizes. Nonionic surfactants with higher HLB values are preferred for spontaneous emulsification and exhibit good oral delivery tolerance [3],[31].

Previous research conducted in the past indicates that oleic acid-and sesame oil-based SNEDDS formulations release drugs at a higher and faster rate than their counterparts based on weaker polar oils. The solubilization of the drug and emulsion composition are theorized to be the reason for the difference in polarity. The selection of emulsifiers in SNEDDS formulations is primarily responsible for determining the size of the formed emulsion globules and the resultant drug bioavailability. For example, smaller and more readily absorbable globules are formed in emulsions with Cremophor than in emulsions with Tween surfactants. Emulsions containing a mixture of PEG 400 and Transcutol have been reported to stabilize SEDDS formulations and improve emulsification rates. However, excess polymers may cause reduced stability by increasing the size of the emulsion droplet, giving rise to a higher risk of phase separation. The improved anti-inflammatory efficacy of diacerein, celecoxib, and curcumin SNEDDS established that the increased dissolution of the drug is a factor in improved bioavailability and hence systemic effects. The best anti-inflammatory effects, characterized by reduced edema and alteration of inflammatory cytokines, were obtained with diacerein, celecoxib, and curcumin SNEDDS, which have oil, surfactant, and co-surfactant in ratios that are scientifically proven to be optimal [1-2],[31].

Common among the various studies are the well-defined characterization strategies. Sampling granule diameter, polydispersity index (PDI), zeta potential, time taken for emulsification, and thermodynamic equilibrium are standard measurements used to confirm the reproducibility and functionality of the formulations. Assessments of inflammation (e.g.,carrageenan-induced inflammation) in clinical and preclinical settings add relevance to these studies [1].

Research surrounding the Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) mostly remains in vitro or in vivo, and in small animal studies, there still remains no significant data regarding human long-term safety or pharmacokinetics. Moreover, the translation of liquid SNEDDS to solid dosage forms has proven particularly difficult in maintaining the same nanoscale attributes, often leading to poor preservation of the desired characteristics. Furthermore, the variety of excipient compositions used across studies leads to significant differences and intricacies that hinder the straightforward comparison of different SNEDDS systems [30],[33-34].

Comparative evidence supports that the optimal selection and ratio of oil, surfactant, and co-surfactant are formulation-dependent and determined by the physicochemical attributes of the active ingredient. Surfactants with high HLB values and hydrophilic cosurfactants produce nanoemulsions with a size distribution of less than 100 nm, which are ideal for improved absorption and distribution across tissues. In contrast, the enhanced permeability and dissolution of the formulation contributed to a greater anti-inflammatory effect. Nevertheless, high amounts of surfactants/cosurfactants can result in GI tolerance issues, hence the need for careful selection (2,30,31). The following is a comparative table between particle size and anti-inflammatory activity, as shown in Table 3.

Table 3. Comparative Table: Droplet Size and Anti-inflammatory Activity of SNEDDS.

Study / drug	Droplet size	Drug release / Bioavailability	Anti-inflammatory outcome	Key observation
Diacerein SNEDDS [1]	Nano-range (measured via DLS, optimized system)	Significantly enhanced dissolution vs pure drug	Significant reduction in paw edema, TNF-α, and caspase-3	Smaller droplet → improved dissolution → enhanced anti-inflammatory effect
Curcumin SNEDDS [23]	~71 nm	High drug loading and improved penetration	~80% reduction in paw edema	Very small droplets correlated with strong anti-inflammatory response

Study / drug	Droplet size	Drug release / Bioavailability	Anti-inflammatory outcome	Key observation
Garlic SNEDDS [24]	<100 nm (uniform droplets)	Increased bioaccessibility (~89%)	Decreased IL-1β expression (↓44.82 AU)	Nano-size improves cellular uptake → cytokine suppression
Garlic SNEDDS – 3T3-L1 cells [25]	~14 nm	Increased bioavailability & stability	Reduced TNF-α & IL-1β, increased IL-10	Smaller droplet size → stronger modulation of inflammatory markers
Piroxicam SNEDDS [26]	<200 nm (nanoemulsion range)	Improved solubility & absorption	Significant reduction in paw edema vs suspension	Nano-droplets enhance pharmacological efficacy
General SNEDDS concept [30]	<100–200 nm	Increased surface area & dissolution rate	Enhanced therapeutic effect	Droplet size is a critical determinant of drug performance

The combination of formulation composition and characterization with biological activity shows that rational SNEDDS design can salvage poorly soluble and membrane-impermeable drugs. Stationary physicochemical attributes, such as globule size and zeta potential, across different studies, are considered indicators of both predictability and activity. This calls for a systems approach with a multiplier effect to be considered in the interactions of the components at different formulation and biological levels [1],[29].

The interactions between different components of SNEDDS occur at several interrelated levels. The first level is the physicochemical interaction between the oil, surfactant, and co-surfactant of the formulation. Oils are mainly used for the solubilization of lipophilic drugs, whereas high HLB surfactants, such as Tween 80 or Cremophor, reduce interfacial tension, leading to spontaneous nanoemulsion formation. Co-surfactants, such as PEG 400 and Transcutol P, increase interfacial flexibility, resulting in the formation of smaller and more homogenous droplets. Essential physicochemical parameters, such as globule size, polydispersity index, and zeta potential, which reflect the stability and predictability of formulations, are critically influenced. Following the discussed article, optimized combinations of these constituents yielded nanoemulsions with enhanced stability and drug release profiles. Recent research suggests that these components interact with each other and contribute to the enhanced performance, which ultimately dictates the efficiency of the SNEDDS system [29-31].

At the biological level, these interactions between formulations also affect drug absorption, distribution, and other functions. Due to its nanoscale droplet size, there is enhanced drug dissolution with rapid drug release potential, resulting in better membrane interactions. Furthermore, lipid-based systems can aid in lymphatic transport and decrease first-pass metabolism. The temporary impact of surfactants on membrane permeability facilitates drug uptake. This interaction is termed a "multiplier effect" meaning that as the physicochemical properties improve, so do the pharmacokinetics of the drug, thus the pharmacodynamics. The cytokines involved in this process are TNF-α and IL-1β, which have anti-inflammatory activity. Nevertheless, any imbalance in these interactions, such as excessive surfactant concentrations, could destabilize the formulation or induce toxicity, which underscores the requirements for a systems-based design approach and recent advances in Quality by Design (QbD) and formulation modelling [29-32].

Numerous challenges remain that significantly slow the advancement of SNEDDS research. These challenges are related to the lack of reliable IVIVC models that can streamline the SNEDDS optimization process early in the clinical translation pathway. It is pivotal to broaden the scope of in vivo studies to address the clinical efficacy and safety of final formulations. The incorporation of multifunctional or new bioresorbable excipients can also optimize the sparing of toxic and adverse effects through better-targeted delivery. In addition, the nanotechnological properties of liquid SNEDDS offer great potential for industrial applications. Therefore, solid SNEDDS are in high demand because they can maintain the beneficial properties of liquid SNEDDS during administration to patients [2],[30],[33].

When we critically appraise the studies reviewed, they show several limitations that ought to be recognized to affirm this systematic review. The majority of studies included were preclinical, relying on small animal and in vitro studies and not translatable to human clinical outcomes, thereby restricting their

generalizability. In addition, formulation design, excipient selection, and evaluation methods show considerable heterogeneity, making cross-study comparisons difficult and hampering the establishment of standard conclusions regarding optimal SNEDDSs performance. The evidence is also weakened by the irregular reporting of important parameters, such as long-term stability, toxicity, and IVIVC. Recent studies have reported some methodological flaws in these papers, such as small sample sizes, lack of standardization, and publication bias for positive results, which may overestimate the effect of SNEDDS formulations [30]–[32]. The presence of variability in excipient quality and the lack of rigorous clinical validation continue to be significant barriers to reproducibility and clinical implementation at scale. Therefore, future SNEDDS studies should prioritize improving the quality of these studies. This can be achieved by following standardized experimental designs, adopting sound statistical analyses, and merging QbD approaches.

▪ CONCLUSION

This review highlights the pivotal role of Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) in addressing the challenges of poor solubility and bioavailability of a range of active pharmaceutical ingredients, especially in anti-inflammatory therapy. The findings consistently indicate that the careful selection and optimal ratio of oils, surfactants, and co-surfactants significantly influence the physical properties, drug release, stability, and biological activity of SNEDDS formulations. Despite substantial progress, several research gaps remain, including the development of predictive in vitro-in vivo correlation models, broader preclinical and clinical validation, and the advancement of robust and scalable techniques for producing solid SNEDDS. Future endeavors should prioritize these areas and the discovery of novel biodegradable excipients to fully realize the therapeutic potential and versatile application of SNEDDS in pharmaceutical development.

Acknowledgements: The authors would like to express their sincere gratitude to all individuals and institutions whose support and contributions were invaluable for the completion of this article.

Funding: No funding agency in the public, commercial, or not-for-profit sectors provided specific funding for this study.

Conflict of interest statement: The authors declare no conflicts of interest.

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