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REVIEW: STABILITY OF SOLID SNEDDS FORMULA IN VARIOUS EXCIPIENTS AND MANUFACTURING METHOD

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ABSTRACT

The stability of Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) remains a significant challenge in oral drug formulation, as liquid SNEDDS often suffer from leakage and chemical instability during storage. Transforming these systems into solid SNEDDS (S-SNEDDS) has emerged as a promising approach to combine the enhanced solubility and bioavailability of nanoemulsified systems with the physical and chemical stability of solid dosage forms. This review comprehensively examines the stability profiles of S-SNEDDS formulations produced using various solidifying agents and manufacturing methods. The discussion focuses on adsorption to solid carriers, spray drying, and freeze-drying techniques while comparing the effects of different adsorbents, such as amorphous silica derivatives Aerosil, Sylysia, and Neusilin, on the stability outcomes. Literature was systematically gathered from databases including PubMed, ScienceDirect, and Google Scholar, covering original studies published between 2011 and 2023 that reported short- and long-term stability. The synthesis of the reviewed data indicates that adsorption onto solid carriers, particularly silica-based excipients, provides the most stable S-SNEDDS formulations. These preparations maintained consistent globule size, drug content, dissolution profile, and absence of phase separation under accelerated and long-term storage conditions. Factors such as high oil absorption capacity and porosity of the adsorbent were key determinants of the flowability and stability of the resulting powder. In conclusion, this review highlights that silica-based adsorbents, especially Sylysia and Neusilin, confer superior stability to S-SNEDDS compared with other materials. The novelty of this study lies in its comparative synthesis of solidification methods, establishing adsorption on amorphous silica as the most robust strategy for producing physically and chemically stable S-SNEDDS formulations.

Keywords: adsorbent; manufacturing method; stability; S-SNEDDS

INTRODUCTION

Oral drug administration remains the preferred route for systemic and local treatments, offering advantages such as ease of use, painless application, and improved patient compliance compared with other modalities, such as injection or inhalation. Despite these benefits, the oral delivery of pharmaceuticals is often hampered by physiological barriers in the gastrointestinal tract, including limited surface area for absorption, enzymatic degradation, and variable transit times, which can result in poor bioavailability and therapeutic variability of several active compounds (Huda & Wahyuningsih, 2016). The emergence of nanotechnology in pharmaceutical sciences, particularly nanoemulsion systems, has provided promising strategies to overcome these barriers, enhancing drug solubility, dissolution rates, and oral bioavailability by leveraging submicron droplet sizes and increased absorption

surface areas. Nevertheless, the chemical and physical stability of nanoparticulate formulations remains a key challenge, necessitating further innovation in drug delivery systems to ensure consistent therapeutic outcomes (Syukri *et al*., 2025; Tanga *et al*., 2026).

This review focuses on the advancement and evaluation of Solid Self-Nanoemulsifying Drug Delivery Systems (S-SNEDDS), a novel class of lipid-based formulations that aim to address the inherent shortcomings of conventional liquid SNEDDS and nanoemulsions in terms of stability and dosing accuracy. The S-SNEDDS system utilizes conversion techniques such as adsorption to porous carriers, spray drying, and freeze-drying to transform liquid nanoemulsions into powder or granule forms, thereby improving their physical stability, ease of handling, dosage precision, and scalability in pharmaceutical manufacturing (Inugala *et al*., 2015; Tarate *et al*., 2014). By focusing on these solid-state transformation methods and their impact on formulation performance, including stability, drug loading, flow properties, and bioavailability, this review synthesizes current research findings on formulation strategies and characterization approaches, aiming to inform the selection of optimal manufacturing techniques and carriers for S-SNEDDS (Syukri *et al*., 2025; Tanga *et al*., 2026).

The use of SNEDDS represents a significant advancement over traditional oral drug delivery vehicles, such as conventional emulsions, tablets, and capsules, which often suffer from limitations in solubility, absorption, and first-pass metabolism. Conventional solid dosage forms, although physically stable, frequently fail to address the poor aqueous solubility and limited bioavailability of lipophilic drugs, as these molecules struggle to dissolve in gastrointestinal fluids and achieve adequate absorption in the gastrointestinal tract. SNEDDS, which consist of isotropic mixtures of oils, surfactants, and co-surfactants, spontaneously form nanoemulsions upon contact with aqueous GI environments, facilitating lymphatic absorption and bypassing hepatic first-pass metabolism (Kuruvila *et al*., 2017; Qomara *et al*., 2023). However, the instability and migration of volatile components in liquid SNEDDS and the lack of robust comparative studies evaluating solidification techniques and carrier performance highlight gaps in the current literature that this review seeks to address by critically appraising solid-state conversion methods and their implications for drug stability and absorption *(Syukri et al*., 2025; Tanga *et al*., 2026).

This review aims to provide a comprehensive analysis of the stability attributes associated with S-SNEDDS, exploring the challenges and benefits of converting liquid SNEDDS into solid preparations using various drying and adsorption methods. The discussion encompasses the selection and optimization of carriers, solidification strategies, and their influence on globule size, polydispersity index (PDI), dissolution, drug content, and long-term stability, which are essential parameters for quality assurance and regulatory compliance in modern pharmaceutical formulations. By consolidating experimental data, formulation case studies, and quality control outcomes from recent literature, this review aims to elucidate the best practices in S-SNEDDS technology and identify future research directions for improving drug bioavailability, stability, and commercial viability (Syukri *et al*., 2025; Tanga *et al*., 2026).

RESEARCH METHOD

The methodology for compiling this review was based on a rigorous and systematic approach appropriate for the field of pharmaceutical technology. Relevant literature was identified through comprehensive searches of major academic databases, including Google

Scholar, PubMed, ScienceDirect, Semantic Scholar, and NCBI. The search strategy utilized specific keywords such as "S-SNEDDS," "adsorbent," "method," and "stability," to ensure that the selected literature addressed the mechanisms, production techniques, and stability considerations of solid self-nanoemulsifying drug delivery systems (S-SNEDDS). Publications considered for inclusion comprised original research articles published in reputable national or international journals, with language restricted to English or Indonesian, and publication dates spanning 2011 to 2025, thereby ensuring both relevance and quality in the data pool.

Tools and Materials

Article curation was facilitated using digital management and search tools, notably Mendeley and Publish or Perish, to streamline the reference and selection processes.

Article Selection Criteria

The inclusion criteria mandated that the selected articles specifically examine the stability of S-SNEDDS in relation to adsorbents and production methodologies, and only primary research articles were considered. The exclusion criteria were strictly implemented, omitting meta-analyses, review articles, systematic reviews, and any papers that were unavailable in full text. This ensured that the synthesis presented in the review was exclusively derived from original empirical evidence, thus increasing its scientific robustness and validity.

Research Procedure

The research article selection procedure followed a multistage process. Initially, database searches were conducted using various modified keyword combinations, followed by a manual search to identify additional relevant sources. The titles of the identified publications were screened for relevance to the research objectives of this study. Subsequently, the abstracts of the selected articles were thoroughly evaluated to ascertain their alignment with the review aims. If the full text of a pertinent article was not immediately accessible, further efforts were made to obtain complete versions through alternative digital repositories and open access platforms. The culmination of this process was the refinement of the results into a body of literature that was both comprehensive and directly applicable to the scope of S-SNEDDS stability studies, as shown in **Figure 1** of the source publication.

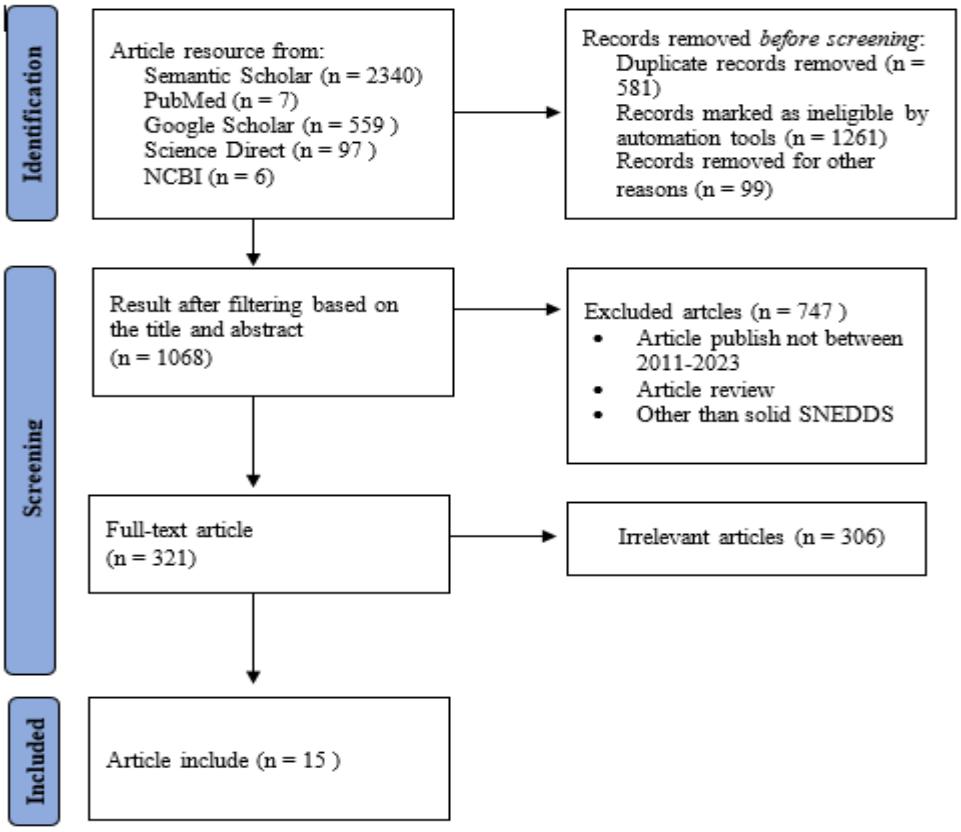

Figure 1. Chart of the literature search procedure

RESULTS AND DISCUSSION

By utilizing search engines, a total of 15 papers were found on the topic of the S-SNEDDS formula, including different manufacturing methods and the outcomes of stability testing. This review discusses three methods for producing S-SNEDDS: adsorption onto a solid carrier, spray drying, and freeze-drying. Each article on the manufacture of S-SNEDDS using a variety of manufacturing methods and drying materials and stability testing carried out is attached in **Table I**.

Table I. Stability of S-SNEDDS formula in various manufacturing methods

Formula SNEDDS	Manufacturing method of S-SNEDDS and Dryer	Stability Testing	Results	Library
Embelin Oil: Capryol 90 Surfactants: Acrysol EL 135 Cosurfactants: PEG 400	Methods: Adsorption to solid carrier Drying Materials: Neusilin and Aerosil 200	Accelerated stability studies (Temperature 40°±5°C/ Relative Humidity (RH) 75 ± 5% for 6 months)	The 6-month accelerated stability test revealed no statistically significant alterations (p>0.05) in the S-SNEDDS test outcomes when using Neusilin desiccant. This includes metrics such as emulsification time, globule size, and drug release during storage. It can therefore be concluded, based on the	(Parmar *et al*., 2015)

			obtained results, that the S-SNEDDS formulation demonstrates satisfactory stability under the tested conditions.	
Hydroclortiazide Oil: Capryol 90 Surfactants: Cremophor RH40 Cosurfactants: Transcutol HP	Methods: Adsorption to solid carrier Desiccant material: Microcrystalline cellulose	Accelerated stability studies (40°C/75% RH for 3 months)	During the stability test, the S-SNEDDS formula using microcrystalline cellulose desiccant showed no significant differences in drug levels and globule sizes compared to other formulas ($p>0.05$). The dissolution test results indicated that the S-SNEDDS formulation remained stable upon dissolution, exhibiting no signs of precipitation or phase separation. The S-SNEDDS preparation obtained is stable.	(Dubey *et al*., 2018)
Efavirenz Oil: Labrafac Surfactants: Tween 80 Cosurfactants: PEG 200	Methods: Adsorption to solid carrier Desiccant material: Aerosil, accurel MP 1000 and porous polystyrene spheres	Accelerated stability studies	The stability test results indicated that the S-SNEDDS formulation exhibited stability, with no notable variations observed in particle size, drug content, and dissolution. The particle size of S-SNEDDS preparations using Aerosil desiccant complied with the acceptable criteria of accurel MP 1000 desiccant and porous polystyrene spheres. The particle size measurements for S-SNEDDS using Aerosil dryer, Acurel MP 1000, and porous polystyrene spheres were 12 nm, 0.2 µm, and 1 µm, respectively.	(Selvam & Kulkarni, 2014)
Q10 Oil: Lauroglycol Surfactants: Labrasol Cosurfactants: Transcutol	Methods: Spray drying Desiccant material: Aerosil	Stability at 5±3°C, 30±2°C/65±5% RH, and 40±2°C/75±5% RH for 3 months	The stability test findings assessed the decline in drug concentrations in liquid SNEDDS (L-SNEDDS) formulations with Aerosil dryer S-SNEDDS under different storage conditions of temperature and	(Akhter *et al*., 2014)

			humidity. The stability test results indicated that the medicine experienced a maximum degradation of 3.13% in both the L-SNEDDS and S-SNEDDS formulations after three months of testing at a temperature of 40 ± 2°C.	
Agomelantin Oil: Isopropyl myristate Surfactants: Labrasol Cosurfactants: Propylene glycol-400	Methods: Adsorption to solid carrier Desiccant material: Talc Powder	Accelerated stability studies (40°C/75% RH for 3 months)	The findings of the accelerated stability test conducted over a period of 3 months indicated that there was no statistically significant difference ($p>0.05$) in the levels of the S-SNEDDS medication. The preparation is in a state of stability.	(Gadhave & Tarkase, 2018)
Simvastatin Oil: Labrasol Surfactants: Cremophor RH40 Cosurfactants: Transcutol P	Methods: Adsorption to solid carrier Desiccant material: Crospovidone	Accelerated stability studies (40°C/75% RH for 6 months)	The findings of the accelerated stability test conducted over a period of 6 months did not reveal any notable differences ($p>0.05$) in the size of the globules, polydispersity index (PDI), and parameters related to the release of the drug. The medication release of simvastatin S-SNEDDS was 84.86 ± 2.08% before 6 months and 84.081 ± 2.21% after 6 months.	(M. S. Reddy & Sowjanya, 2015)
1-palmitoyl-2-linoleoyl-3-acetyl-rac-glycerol (PLAG) Oil: PLAG Surfactants: Sodium lauryl sulfate (SLS) Cosurfactants: Hydroxypropyl methylcellulose (HPMC)	Methods: Spray drying Desiccant material: Calcium silicate	Stability of drug content at 60°C for 5 days Thermodynamic stability Heating-cooling test (45 and 4°C) Freeze thaw cycle (-21 and 25°C) Centrifugation stress	Stability testing of drug levels at a temperature of 60 °C for a duration of 5 days revealed that both pure active ingredients and commercial formulations exhibited a drop of around 30%. However, S-SNEDDS did not demonstrate any significant differences ($p>0.05$). The thermodynamic stability of the S-SNEDDS preparation was confirmed using various tests, including heating-cooling, freeze-thaw cycle, and centrifugation, which showed no phase separation. The S-	(Kim *et al.*, 2017)

			SNEDDS formulation is categorized as stable.	
Adefovir dipivoxil Oil: Capmul Surfactants: Tween 60 Cosurfactants: PEG 200	Methods: Freeze drying Drying Materials: D-mannitol	Accelerated stability studies (40±2°C/75±5% RH for 3 months) Long term stability studies (30±2°C/65±5% RH)	There were no changes in the organoleptic results and zeta potential of L-SNEDDS and S-SNEDDS preparations under two storage conditions. The Adefovir levels did not show a notable decline, indicating that the S-SNEDDS with D-mannitol desiccant is chemically stable.	(Gupta *et al.*, 2011)
Nebivolol HCl Oil: Capmul Surfactants: Tween 60 Cosurfactants: PEG 400	Methods: Freeze Drying Drying Materials: D-mannitol, trehalose, lactose	Stability test 25°C/60% RH Accelerated stability studies 40±2°C/ 75±5% RH for 3 months	Stability tests conducted under two different settings demonstrated that S-SNEDDS including D-mannitol desiccant yielded globule and emulsion sizes that met the required standards, in contrast to S-SNEDDS using trehalose and lactose desiccants. There was no significant change in the zeta potential value and medication content during stability tests under the two storage settings.	(Narkhede *et al.*, 2014)
Valsartan Oil: Capmul Surfactants: Labrasol Cosurfactants: Tween 20	Methods: Adsorption to solid carrier Drying Materials: Aerosil 200, Sylysia 350, 550, 730 and Neusilin US2	Accelerated stability studies (40°C/75%RH for 6 months)	As the grade of Sylysia dryer increases, its capacity to absorb oil decreases, resulting in suboptimal formation of S-SNEDDS and reduced stability of the preparation. A S-SNEDDS formulation utilizing a Sylysia 350 dryer exhibits comparable granule size and drug content to that of alternative dryers.	(Beg *et al.*, 2012)
Sertraline Oil: Labrafil and Maisine 35-1 in 1:1 ratio] Surfactants: Tween 80 Cosurfactants: Lauroglycol 90	Methods: Spray drying Desiccant material: Dextran 40	Accelerated stability studies (40°C/75%RH for 3 months)	The surface characterization (SEM) of S-SNEDDS with Dextran 40 desiccant was superior to that of sucrose and maltodextrin desiccants. There were no notable alterations in particle size and PDI observed	(Rahman *et al.*, 2016)

			throughout the stability testing procedure.	
Glimepirid Oil: Miglyol Surfactants: Tween 80 Cosurfactants: PEG 400	Methods: Adsorption to solid carrier Drying Materials: Aerosil 200 (Dioxosilane)	Accelerated stability studies (40°C/75%RH for 3 months)	The stability testing of S-SNEDDS preparations revealed no statistically significant change ($p>0.05$) in the results of globule size, PDI, dissolution, and drug levels before and after storage. The f2 similarity factor result for S-SNEDDS with Aerosol 200 drier is 94.51%, indicating a high level of similarity in dissolution values before and after storage.	(Mohd *et al.*, 2015)
Nelfinavir mesylate Oil: Maisine 35-1 Surfactants: Cremophor RH 40 Cosurfactants: Labrasol	Methods: Adsorption to solid carrier Drying Materials: Aerosil 200, Lactose and Neusilin US2	Accelerated stability studies (40±2 °C/ 75 %±5 % RH for 3 months)	The combination of S-SNEDDS with Neusilin US2 desiccant exhibited superior adsorption capacity and resulted in the production of powders that flowed freely. In comparison, Aerosil 200 and Lactose desiccant did not perform as well in terms of adsorption capacity and powder flow. The Nelfinavir S-SNEDDS formulation, when combined with Neusilin US2 desiccant, exhibited negligible alterations in globule size (10-12%), percent transmittance (97-98%), and drug content (96-98%), indicating its stability. Subsequently, the L-SNEDDS formulation exhibited leakage and instability following a storage period of 1 month.	(Patel *et al.*, 2014)
Rilpivirin Oil: PEG 400 and propylene glycol Surfactants: Cremophor RH40 Cosurfactants: Transcutol 90	Methods: Adsorption to solid carrier Drying Materials: Neusilin US2	Accelerated stability studies (40°C/75%RH for 1 month)	Following a storage period of one month, the droplet size and PDI values remained consistent at 16.27 nm and 0.276, respectively, suggesting no notable alterations throughout the stability testing. The percentage composition of Rilpivirin S-SNEDDS remained unchanged	(B. S. Reddy *et al.*, 2016)

			(p>0.05), suggesting that the formula for Rilpivirin S-SNEDDS is stable.	
Aprepitan Oil: Imwitor Surfactants: Capryol Cosurfactants: Transcutol	Methods: Adsorption to solid carrier Drying Materials: Soluplus, PVP/VA (Kollidon VA64), PVP (Kollidon 25) and HPMC (Methocel E5)	Accelerated Stability Studies (40±2 °C/ 75 %±5 % RH for 6 months) Long term stability studies (25±2°C/60±5% RH)	The rapid and long-term stability testing findings for Aprepitan drug release indicated that over 85% (Q + 5%) of the active component dissolved within 30 minutes for a duration of 6 months. The test results indicated that there was no statistically significant difference (p>0.05) in the release of the medication before and after stability testing.	(Nazlı *et al.*, 2023)

Solid self-nanoemulsifying drug delivery systems (S-SNEDDS) have become an increasingly important focus in pharmaceutical technology research, addressing the biopharmaceutical limitations of many active pharmaceutical ingredients, especially those with low aqueous solubility. This review synthesizes findings from the past five years on various manufacturing techniques, carrier selection, and stability testing methods relevant to S-SNEDDS. Specifically, it evaluates the comparative advantages and constraints of adsorption onto solid carriers, spray drying, and freeze-drying processes, offering a critical cross-study perspective for future formulation design (Buddhadev *et al*., 2025; Syukri *et al*., 2025; Tanga *et al*., 2026).

Adsorption onto solid carriers is the most widely implemented technique because of its operational simplicity and flexibility to accommodate a range of desiccants, such as Neusilin US2, Aerosil 200, and Sylysia 350. These silica-based materials are preferred because of their high oil absorption capacity, physicochemical stability, and ability to yield dry, free-flowing powders. Recent studies have utilized microcrystalline cellulose, talc powder, crospovidone, and dextran 40 as alternative desiccants, expanding the applicability of this technique across different drug and excipient profiles. Spray drying leverages rapid solvent evaporation, which is advantageous for producing uniform, flowable S-SNEDDS but may pose challenges for actives that are sensitive to elevated temperatures. Freeze-drying, or lyophilization, is comparatively resource-intensive but remains the method of choice for heat-labile actives and ensures the preservation of nanoemulsion integrity in the dry state (Krstic *et al*., 2018; Patel *et al*., 2014).

Across studies, solid carriers, especially highly porous silicas, consistently yield robust S-SNEDDS stability profiles under ICH-recommended accelerated and long-term storage conditions (typically 40°C/75% RH and 30°C/65% RH, respectively). For example, Parmar *et al*. (2015) and Patel *et al*. (2014) demonstrated that Neusilin US2 and Sylysia 350 maintain drug content, droplet size, and dissolution properties with negligible changes over months, outperforming less porous or more hydrophilic alternatives, such as lactose. Spray drying, as evidenced by Kim *et al*. (2017), enables the fast conversion of L-SNEDDS to solid forms; stability tests for PLAG and Q10 SNEDDS using calcium silicate and Aerosil produced results where only minor losses in drug content (under 5%) were observed after multiple months of storage. Meanwhile, freeze-dried systems utilizing D-mannitol or trehalose effectively stabilized sensitive APIs such as Adefovir Dipivoxil and Nebivolol HCl (Gupta *et al*., 2011; Narkhede *et al*., 2014), maintaining organoleptic and zeta potential parameters throughout rigorous temperature and humidity cycling.

The rationale for desiccant selection is based not only on their oil adsorption and flow enhancement capacity but also on their compatibility with the active pharmaceutical ingredient. Silica derivatives, such as Sylysia 350, exhibit a hierarchical pore structure, maximizing their oil-holding capability, thus producing S-SNEDDS powders with superior stability and processability. Drug properties, notably lipophilicity and sensitivity to heat or moisture, inform both carrier and process selection. For instance, carrier-based adsorption is highly suited to heat-sensitive drugs, whereas the drying parameters in spray drying must be carefully modulated for thermolabile actives. Furthermore, the chemical nature of the carrier can affect drug-carrier interactions, affecting both drug release kinetics and physical stability. Non-silica carriers, such as crospovidone or dextran, can be employed for APIs that present compatibility challenges with standard silica, but may require additional flow aids or anti-caking agents to optimize powder characteristics (Syukri *et al*., 2025; Tanga *et al*., 2026).

A significant strength of silica-based solid carriers is their reproducible performance in maintaining S-SNEDDS stability. However, the literature consistently identifies the need for individualized optimization, as not all drugs benefit equally from any given desiccant. For example, Nelfinavir with Neusilin US2 demonstrated excellent physical and chemical stability, whereas the same formulation with lactose showed instability and poor powder flow. The main limitations of spray drying are residual solvent retention, the potential for incomplete drying, and the risk of exposing actives to unsuitable thermal stress. Although freeze-drying stabilizes, it is slower and more expensive, potentially limiting its scalability for routine industrial production (Buddhadev *et al*., 2025; Syukri *et al*., 2025).

Despite rigorous advances, direct head-to-head comparative studies between all available process-carrier combinations remain rare, resulting in variability in the reported performance metrics across the S-SNEDDS landscape. Much recent work has focused on short-term accelerated testing; however, the correlation between these results and the actual shelf life under ambient conditions is not always linear, especially for more complex multi-drug S-SNEDDS (Buddhadev *et al*., 2025). Additionally, in silico and machine-learning approaches hold promise for carrier selection and process parameter optimization, but have not been widely validated using large, diverse datasets.

Future research should focus on conducting systematic and comparative investigations of adsorption, spray drying, and freeze-drying techniques using standardized model APIs and comprehensive excipient libraries. Such efforts will enable meaningful cross-comparisons of the formulation strategies. Equally important is the integration of solid-state characterization methods, including PXRD, DSC, and SEM, with empirical stability and dissolution data, creating a bridge between chemical, physical, and functional stability outcomes under real-world conditions. Moreover, advancing predictive modeling approaches that combine quality-by-design (QbD) principles with machine learning frameworks will be essential to rationally guide S-SNEDDS design from the molecular to the manufacturing scale. Finally, future studies should emphasize patient-centric considerations, including palatability, capsule compatibility, and in vivo absorption correlations, particularly within the context of multi-component drug delivery systems (Buddhadev *et al*., 2025; Syukri *et al*., 2025).

CONCLUSION

The collected literature demonstrates that converting liquid SNEDDS into solid forms (S-SNEDDS) significantly enhances the formulation stability, handling, and storage performance. Among the various solidification methods reviewed—adsorption, spray drying, and freeze drying—adsorption onto silica-based carriers, particularly Sylysia and Neusilin, consistently exhibited superior outcomes in maintaining droplet size, drug content, dissolution behavior, and the absence of phase separation during accelerated and long-term stability studies. The high oil absorption capacity and porous architecture of these materials are critical for achieving uniform, free-flowing powders with reproducible stability profiles. Although spray drying and freeze-drying offer viable alternatives, their operational complexity and cost present limitations for large-scale production. Overall, this comparative synthesis underscores adsorption-based solidification as the most robust, efficient, and

scalable approach for improving the physical and chemical stability of S-SNEDDS formulations, facilitating their broader applicability in enhancing the oral bioavailability of poorly soluble drugs.

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