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Strategy for enhancing stability and bioavailability of active lipid ingredients through nanoparticle technology: Review

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ABSTRACT

Background: Lipid-based active ingredients have high pharmacological potential, such as anti-inflammatory, antioxidant, and anticancer activities, but often face biopharmaceutical challenges such as low water solubility, poor chemical stability, and limited bioavailability. Objectives: This review article aims to analyze various nanoparticle technology-based formulation strategies to improve the stability and pharmacological activity of lipid active ingredients. Methods: A total of 31 scientific articles published between 2020 and 2025 were systematically analyzed to evaluate the types of lipid nanoparticle systems, production methods, the role of surfactants and additives, and their impact on stability and bioavailability. Commonly used systems include *Solid Lipid Nanoparticles* (SLN), *Nanostructured Lipid Carriers* (NLC), and nanoemulsions. Results: The results of the study indicate that encapsulation in a nano lipid matrix can protect the active ingredients from oxidative, photolytic, and enzymatic degradation and increase membrane solubility and permeability. Key factors for successful formulation include the selection of lipid type, production method, and the combination of surfactant and coating polymer. In addition to improving pharmacokinetic parameters, lipid nanoparticle systems also show potential for cost efficiency through dose reduction and increased therapeutic efficacy. Conclusions: Overall lipid nanoparticle technology is an effective, applicable and prospective approach in the development of modern pharmaceutical preparations based on lipophilic active ingredients.

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INTRODUCTION

Lipid- or lipophilic-based active ingredients possess broad pharmacological potential, including anti-inflammatory, antioxidant, anticancer, and hepatoprotective activities. Compounds such as curcumin, coenzyme Q10, vitamin E, and various flavonoids demonstrate significant biological efficacy in various disease models. However their physicochemical characteristics, including poor

water solubility, are a major obstacle in the development of conventional pharmaceutical preparations. Poor solubility directly impacts limited gastrointestinal dissolution and poor oral bioavailability (Sambhakar et al., 2023). Therefore formulation strategies that can overcome these biopharmaceutical limitations are needed.

In addition to solubility issues, lipid active ingredients are also susceptible to chemical degradation such as oxidation, hydrolysis, and exposure to light and temperature. This degradation not only reduces the active ingredient content but can also reduce therapeutic efficacy and shorten the product's shelf life. In biological systems, lipophilic compounds can also undergo rapid metabolism, further reducing the fraction of drug reaching systemic circulation. This challenge demands technological approaches capable of providing physical and chemical protection to the active molecules (Ashfaq et al., 2023). Therefore stability is a key parameter in the development of lipid-based dosage forms.

The development of nanotechnology in the pharmaceutical field offers innovative solutions to enhance the performance of lipid active ingredients. Nanoparticles allow for increased specific surface area, thereby accelerating dissolution and enhancing absorption. Furthermore, nanosystems can be designed to provide controlled release and increase drug residence time at the target site. The role of nanoparticles in modern drug delivery systems is increasingly important due to their ability to increase therapeutic efficacy and reduce side effects (Joseph et al., 2023). Therefore nanoparticle technology is becoming a strategic approach in the formulation of lipophilic drugs.

One of the most widely developed systems is lipid-based nanoparticles, such as *Solid Lipid Nanoparticles* (SLN) and *Nanostructured Lipid Carriers* (NLC). SLN use solid lipids as a carrier matrix, while NLCs combine solid and liquid lipids to enhance drug entrapment capacity. NLCs were developed to overcome the limitations of SLNs, particularly the risk of recrystallization and low entrapment efficiency. Both systems have been shown to improve the stability and bioavailability of various lipophilic compounds (Musielak et al., 2022; Viegas et al., 2023). With these characteristics, lipid nanoparticles are a promising platform for drug delivery. Although several previous reviews have comparatively discussed SLN and NLC systems, most focused primarily on structural differences and general performance parameters without integrating recent translational, pharmacoeconomic, and clinical-oriented findings.

The lipid nanoparticle production method also plays a critical role in determining the final characteristics of the system. Techniques such as high-pressure homogenization, ultrasonication, and microemulsion methods have been widely used at both laboratory and industrial scales. Each method has advantages and limitations related to particle size, entrapment efficiency, stability, and potential scalability. The choice of production method must consider the properties of the active ingredient and the desired therapeutic objective (Mehta et al., 2023). With proper process optimization, nanoparticle systems can be produced consistently and sustainably. However, emerging studies from 2020–2025 highlight the importance of process scalability, industrial reproducibility, and regulatory considerations, aspects that remain insufficiently synthesized in earlier comparative reviews.

In addition to lipids and production methods, surfactants and excipients play a crucial role in system stability. Surfactants such as Poloxamer 188, Tween 80, and lecithin lower interfacial tension and prevent particle aggregation. The addition of coating polymers such as chitosan and *polyethylene glycol* (PEG) can increase circulation time and tissue targeting ability. This combination of components also contributes to the controlled regulation of drug release profiles (Jacob et al., 2022). Recent literature also emphasizes multifunctional surface engineering strategies, including mucoadhesive and stealth modifications, which were not comprehensively compared in earlier SLN versus NLC reviews.

Various studies have shown that lipid nanoparticle systems not only enhance stability but also improve pharmacokinetic parameters and therapeutic response. Increased bioavailability of

curcumin, vitamins, and anticancer drugs has been reported in various in vitro and in vivo studies. Furthermore, these systems have the potential to reduce dosing frequency and improve patient compliance. These advantages make lipid nanoparticles a relevant strategy in the development of modern pharmaceutical preparations (Rehman et al., 2024). Therefore, the novelty of this review lies in integrating comparative physicochemical performance, recent formulation engineering advances (2020-2025), translational potential, and pharmacoeconomic implications into a unified synthesis, thereby addressing gaps not fully explored in previous SLN and NLC comparative reviews.

RESEARCH METHOD

This study was designed as a systematic literature review aimed at analyzing strategies for increasing the stability and bioavailability of lipid active ingredients using nanoparticle technology. The research process was conducted chronologically, starting from the formulation of research questions, determining inclusion and exclusion criteria, and synthesizing data in a narrative-descriptive manner. A literature search was conducted in three major databases, namely PubMed, Scopus, and Google Scholar, with a publication year range of 2020-2025. Keywords used included combinations of terms such as "*lipid active ingredients*", "*lipid nanoparticles*", "SLN", "NLC", "*bioavailability*" and "*drug stability*". Inclusion criteria included in vitro and in vivo research articles, as well as experimental formulation studies evaluating the stability or pharmacological activity of nanoparticle-based lipid active ingredients. Non-peer-reviewed articles, duplicates, and studies outside the pharmaceutical field were excluded from the analysis. To minimize publication bias, the search strategy included broad keyword combinations, manual screening of reference lists from selected articles (snowballing technique), and inclusion of studies reporting both positive and negative outcomes related to nanoparticle performance. Additionally, database searches were not limited by publisher or country to avoid regional bias.

The research procedure was carried out systematically with the following stages: (1) literature identification through database searches using predetermined keywords, (2) removal of duplicate articles, (3) screening of titles and abstracts based on topic relevance, (4) full-text evaluation according to inclusion and exclusion criteria, (5) extraction of primary data from selected articles, and (6) analysis and synthesis of results. The stages in Figure 1 were carried out to ensure transparency, reproducibility, and consistency in the literature selection process. To further reduce selection bias, the screening and eligibility assessment were performed independently by two reviewers, and disagreements were resolved through discussion until consensus was reached.

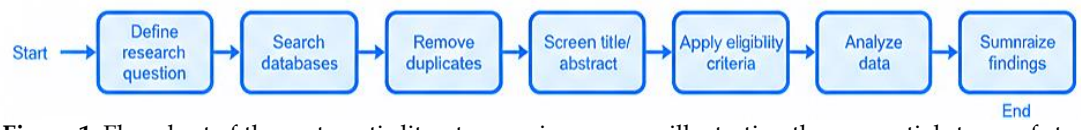

Figure 1. Flowchart of the systematic literature review process illustrating the sequential stages of study identification, screening, eligibility assessment, data extraction, analysis and synthesis of findings

Data analysis and acquisition were conducted by extracting key parameters from each article that met the criteria, including lipid active ingredient type, nanoparticle type (SLN, NLC, or other), production method, particle size, zeta potential, entrapment efficiency, drug release profile, and stability and bioavailability data. Quantitative data were compared descriptively to identify trends in stability improvement and therapeutic efficacy, while qualitative data were analyzed narratively to assess the most influential formulation factors. Information validity was maintained by using only full-text articles from reputable, peer-reviewed journals. The methodological quality and risk of bias of the 31 analyzed articles were assessed using adapted critical appraisal criteria based on study design, clarity of experimental methodology, completeness of physicochemical

characterization, reproducibility of results, and transparency of statistical analysis. Each study was categorized as low, moderate, or high risk of bias according to the completeness of reported parameters and internal consistency of findings. The final results were synthesized in the form of comparative tables and thematic discussions to provide a comprehensive overview of the effectiveness of lipid nanoparticle technology in enhancing the performance of lipophilic active ingredients.

RESULTS AND DISCUSSIONS

Effect of Lipid Nanoparticles on Stability Enhancement

The results in Table 1 show that lipid nanoparticle technology consistently improves the chemical and physical stability of lipophilic active ingredients. Encapsulation in a solid lipid matrix in the *Solid Lipid Nanoparticles* (SLN) system is able to protect compounds from oxidative and photolytic degradation by limiting direct contact with oxygen and light. A study by (Shrestha et al., 2021) reported that phytostanol esters in the SLN system showed resistance to oxidation in a simulated gastrointestinal tract. Furthermore, the stability of vitamin B2 in the lipid nanoparticle system was also increased against heat and light exposure (Hrubša et al., 2022). These findings indicate that the lipid matrix structure acts as an effective protective barrier.

Table 1. Improved stability of lipid actives via nanoparticle formulations

Reference	Active Ingredients	Types of Nanoparticles	Results
(Shrestha et al., 2021)	Phytostanol ester	SLN	Stable in GIT simulation, oxidation resistant
(Talarico et al., 2021)	Quercetin	SLN via coacervation	Controlled release up to 12 hours
(Hrubša et al., 2022)	Vitamin B2	SLN	Resistance to light and heat increases
(Simao et al., 2020)	Flavanone	Lipid nanocarrier	Stable for 1 month without significant degradation
(Subroto et al., 2022)	Ferrous sulfate	SLN via double emulsion	Stable at 4°C and 25°C

Nanostructured Lipid Carriers (NLC) systems exhibit additional advantages over SLNs due to their more irregular matrix structure, which increases entrapment capacity and maintains stability during storage. (Viegas et al., 2023) explained that the combination of solid and liquid lipids in NLCs reduces the risk of recrystallization, which can lead to drug leaching from the matrix. The imperfect or less-ordered crystalline structure of NLC matrices creates structural voids and lattice imperfections that accommodate drug molecules more efficiently, thereby minimizing drug expulsion during lipid polymorphic transitions. Data compiled in various studies indicate a decrease in active ingredient degradation of less than 10% during 3-6 months of storage in nanoparticle formulations, compared to more than 30% in conventional preparations (Rahmasari et al., 2022). By preventing tight lipid packing and crystal rearrangement, NLC systems reduce the thermodynamic driving force for drug migration to the particle surface, which is a primary mechanism underlying drug expulsion in highly ordered SLN matrices. Thus, NLC systems offer advantages in long-term stability.

Improvement of Bioavailability and Pharmacological Activity

In terms of bioavailability, most studies report significant improvements after the active ingredient is formulated in lipid nanoparticles. (Murthy et al., 2020) showed that raloxifene in an NLC system experienced a 2.3-fold increase in bioavailability compared to the conventional form. This increase is related to the nanoparticle size (<200 nm), which increases the surface area and accelerates dissolution. Furthermore, the lipid system can increase mucosal permeability and prolong drug residence time in the gastrointestinal tract (Thuy et al., 2022). The enhancement of mucosal permeability by surfactants such as Tween 80 may alter membrane fluidity and tight junction integrity, facilitating transcellular and paracellular transport; pharmacokinetically, this can result in increased *absorption rate* (Ka), higher *maximum plasma concentration* (Cmax), and expanded *area under the curve* (AUC), potentially modifying drug distribution and systemic

exposure. Overall, lipid nanoparticles improve pharmacokinetic parameters such as AUC and peak plasma concentration.

Pharmacological effectiveness is also significantly enhanced in various disease models. Rapalli et al. (2020) reported increased skin retention and anti-inflammatory activity of curcumin in an NLC system compared to a standard preparation. In ophthalmic applications, (Yadav et al., 2020) demonstrated that SLN as eye drops enhanced the effectiveness of macular degeneration therapy by increasing tissue penetration and retention. Meanwhile, (Mittal et al., 2023) demonstrated that NLC-temozolomide enhanced anticancer activity and reduced systemic toxicity. Clinically, a 2–3-fold increase in bioavailability may allow dose reduction while maintaining therapeutic plasma concentrations, thereby decreasing the risk of dose-related adverse effects and improving safety margins; however, such adjustments require careful pharmacokinetic evaluation to avoid unintended toxicity due to higher systemic exposure. These results confirm that lipid nanoparticle systems not only enhance stability but also therapeutic response.

Role of Surfactants and Additives

Comparative analysis shows that system success is greatly influenced by the choice of surfactant and excipients. (Jacob et al., 2022) explained that surfactants such as Poloxamer 188 and Tween 80 play a crucial role in producing a narrow particle size distribution and preventing aggregation. The addition of coating polymers such as PEG increases circulation time and reduces immune system recognition. Furthermore, chitosan, as a cationic coating, enhances mucosal adhesion and drug permeation (Javed et al., 2023). This combination of components synergistically supports system stability and drug delivery efficiency.

Production Methods and Scalability

The research results also show that the production method significantly influences the final characteristics of nanoparticles. *High-pressure homogenization* (HPH) is the most widely used method because it produces particles of consistent size and is suitable for industrial scale (Mehta et al., 2023). However this method requires a high investment in equipment. Alternatives such as ultrasonication and solvent evaporation are simpler at the laboratory scale but have limitations in size consistency and the use of organic solvents (Manickam et al., 2023). Therefore the choice of method must consider the balance between efficiency, stability, and production scalability.

Clinical and Therapeutic Implications

Clinically, lipid nanoparticle systems show broad potential across various routes of administration, including oral, topical, and parenteral. (Rehman et al., 2024) confirmed that lipid-based nanoformulations can enhance drug delivery effectiveness while reducing dosing frequency. Studies on curcumin and vitamin E showed significant increases in antioxidant and anti-inflammatory activity after formulation in lipid nanosystems (Izadi et al., 2024). Furthermore, their application in the treatment of non-alcoholic fatty liver disease demonstrated enhanced hepatoprotective potential through improved stability and absorption (Yakubu & Pandey, 2024).

Evaluation of the Application of Lipid Nanoparticle Technology in Active Ingredient Formulations

Based on the analysis in Table 2, the application of lipid nanoparticle technology demonstrates significant pharmacoeconomic implications from various perspectives, including the public health system, society, and the pharmaceutical industry. Most studies report that the use of SLN and NLC can reduce dosage requirements, improve stability during storage, prolong drug release time, and reduce the frequency of administration. Clinical impacts include improved patient compliance, reduced relapse rates, and long-term cost-efficiency in treatment. For example, the SLN-ferrous sulfate formulation demonstrated better gastrointestinal tolerability than conventional therapy, while SLN-ketoconazole accelerated the healing of skin infections with a

lower application frequency (Mall et al., 2024). This confirms that improved formulation performance directly contributes to therapeutic efficiency.

Furthermore, NLC formulations such as temozolomide for melanoma and brimonidine for topical ophthalmic therapy have demonstrated increased therapeutic efficacy with reduced systemic toxicity, thus supporting more cost-effective treatments. The use of excipients such as PEG and chitosan has also been shown to improve bioavailability and extend the shelf life of products, ultimately strengthening the economic value of nanoparticle systems. Overall, lipid nanoparticle-based formulations are considered more cost-effective than conventional preparations because they optimize the amount of active ingredients, prolong product stability, and improve clinical outcomes without significantly increasing costs. Therefore this technology has broad prospects for implementation in modern healthcare systems, for both acute and chronic therapy (Mehta et al., 2023).

Table 2. Evaluation of cost-effectiveness for lipid-based active ingredient formulations using nanoparticle technology

Reference	Medication Used	Adherence and Outcome Factors	Qualitative Cost-Effectiveness Assessment	Overall Conclusion on Cost-Effectiveness
(Subroto et al., 2022)	SLN-ferrous sulfate	Improved GI tolerance, higher patient compliance	SLN reduces costs due to better tolerability and less dropout	SLN-ferrous is more cost-effective than conventional oral iron
(Sadozai et al., 2022)	SLN-ketoconazole	Better skin absorption, reduced application frequency	SLN reduces treatment duration and recurrence rate	SLN-antifungal more cost-effective with improved patient outcomes
(Rohmah et al., 2022)	NLC-vitamin E + β-carotene	Higher stability and shelf life, better cell viability	Lower dose required, reduced loss during storage	NLC combination is economically superior to single vitamin formulations
(Elmowafy & Al-Sanea, 2021)	SLN-diclofenac	Faster inflammation reduction, better patient-reported outcomes	Less medication required, better symptom control	SLN gel is economically preferred for anti-inflammatory therapy
(Yadav et al., 2020)	NLC-brimonidine	Longer retention time, increased ocular bioavailability	Reduced dosage frequency, enhanced quality of life	NLC ophthalmic treatment reduces long-term management costs of AMD
(Mittal et al., 2023)	NLC-temozolomide	Lower systemic toxicity, improved survival outcomes	Improved efficacy at lower cost	NLC-temozolomide is highly cost-effective for advanced melanoma
(Zhang et al., 2022)	PEG-NLC-curcumin	Improved stability and enhanced oral bioavailability	Cost-effective due to enhanced absorption and fewer side effects	PEG-NLC offers better cost-effectiveness for chronic oral therapy
(Rapalli et al., 2020)	NLC-curcumin	Higher antioxidant effect, less dosage required	Higher therapeutic index with minimal waste	NLC-curcumin is a cost-saving antioxidant therapy
(Singh et al., 2020)	SLN-vitamin B2	Photostability and heat resistance improve storage logistics	Reduces inventory loss due to degradation	SLN-vitamin B2 lowers storage and distribution costs
(Afra et al., 2020)	SLN-flavonoid extract	Better heart protection at lower dosage	Reduces hospitalization and medication costs	SLN-flavonoid provides better economic value in ischemic heart therapy
(Yakubu & Pandey, 2024)	Curcumin	Anti-inflammatory, antioxidant, reduces liver fat, improves insulin sensitivity	Low solubility and bioavailability	NLC/SLN improves stability and absorption
(Samrit et al., 2024)	Sacha Inchi Oil	Rich in omega-3, reduces triglycerides, oxidative stress and hepatic inflammation	Oxidation-prone, limited absorption	Lipid nanoparticles protect and enhance delivery

Overall, the study results indicate that lipid nanoparticle technology is an effective, adaptive, and relevant strategy for the development of modern pharmaceutical preparations based on lipophilic active ingredients.

CONCLUSION

Based on the findings, the objective of analyzing strategies to enhance the stability and bioavailability of lipid active ingredients through nanoparticle technology has been achieved. SLN and NLC systems improve protection against degradation, enhance solubility and permeability, and positively influence pharmacokinetic parameters and therapeutic outcomes. To bridge the gap between preclinical evidence and late-phase clinical trials, future research should prioritize standardized scale-up protocols, long-term stability validation, comprehensive pharmacokinetic-pharmacodynamic (PK-PD) modeling, and well-designed randomized clinical studies. An integrative translational model linking formulation variables (lipid composition, particle size, surfactant system) to stability performance, bioavailability enhancement, pharmacokinetic modulation, and ultimately clinical outcomes can serve as a structured framework for future development and regulatory evaluation.

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