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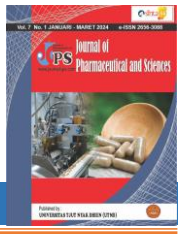

Advanced Drug Delivery Systems: Nano-Formulation Challenges of Poorly Water-Soluble Phytochemicals

Sistem Penghantaran Obat Mutakhir: Tantangan Formulasi Nano untuk Fitokimia yang Sulit Larut dalam Air

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Abstract

The poor water solubility and low oral bioavailability of various phytochemical compounds (BCS Classes II and IV) continue to be major obstacles in the development of modern therapeutics, despite their remarkable therapeutic potential. This narrative review critically evaluates the use of nanoscale drug delivery systems to overcome the biopharmaceutical limitations of hydrophobic phytochemicals and pinpoints key challenges in clinical translation and industrial-scale production. The review provides a comprehensive analysis of the latest literature on the effectiveness of nanotechnology-based physicochemical modifications, including solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanosuspensions, polymeric micelles, liposomes, and phytosomes. The review's results indicate that nano-carrier engineering significantly enhances solubility, avoids first-pass metabolic degradation, and enables targeted delivery. Specifically, nanoformulations have proven effective at penetrating the dense matrix of the tumor microenvironment (TME) in cancer therapy, crossing the blood-brain barrier (BBB) in neurodegenerative diseases, and protecting drugs from stomach acid in infectious and metabolic conditions. However, the transition toward commercialization is hindered by issues of long-term physicochemical stability (e.g., lipid polymorphic transitions) and challenges in standardizing botanical raw materials. These issues affect the reproducibility of large-scale production, ultimately delaying the availability of these promising therapies to patients in need. In conclusion, while nanoformulations offer transformative solutions for overcoming phytochemical biological barriers, standardizing protocols, innovating green synthesis, and fostering interdisciplinary collaboration are essential for overcoming scalability barriers and preparing these innovations for clinical application.

***Keywords*: Phytochemistry; Nanodelivery systems; Bioavailability; Clinical translation; Industrial scale**

Abstrak

Kelarutan air yang rendah dan bioavailabilitas oral yang rendah dari berbagai senyawa fitokimia (Kelas BCS II dan IV) masih menjadi hambatan utama dalam pengembangan terapi modern, meskipun senyawa tersebut memiliki potensi terapeutik yang sangat menjanjikan. Tinjauan naratif ini secara kritis mengevaluasi penggunaan sistem penghantaran obat berskala nano untuk mengatasi keterbatasan biofarmasetika fitokimia hidrofobik serta mengidentifikasi tantangan utama dalam translasi klinis dan produksi skala industri. Tinjauan ini memberikan analisis komprehensif terhadap literatur terbaru mengenai efektivitas modifikasi fisikokimia berbasis nanoteknologi, termasuk nanopartikel lipid padat (Solid Lipid Nanoparticles/SLNs), pembawa lipid terstruktur nano (Nanostructured Lipid Carriers/NLCs), nanosuspensi, misel polimerik, liposom, dan fitosom. Hasil tinjauan menunjukkan bahwa rekayasa nano-pembawa secara signifikan meningkatkan kelarutan, menghindari degradasi metabolik lintas pertama (*first-pass metabolism*), serta memungkinkan penghantaran obat yang lebih terarah. Secara khusus, nanoformulasi terbukti efektif dalam menembus matriks padat lingkungan mikro tumor (*Tumor Microenvironment/TME*) pada terapi kanker, melintasi sawar darah otak (*Blood-Brain Barrier/BBB*) pada penyakit neurodegeneratif, serta melindungi obat dari asam lambung pada kondisi infeksi dan metabolik. Namun, proses transisi menuju komersialisasi masih terhambat oleh masalah stabilitas fisikokimia jangka panjang (misalnya transisi polimorfik lipid) dan tantangan dalam standarisasi bahan baku botani. Permasalahan ini memengaruhi reproduktibilitas produksi skala besar sehingga pada akhirnya memperlambat ketersediaan terapi yang menjanjikan ini bagi pasien yang membutuhkan. Sebagai kesimpulan, meskipun nanoformulasi menawarkan solusi transformatif untuk mengatasi hambatan biologis fitokimia, standarisasi protokol, inovasi sintesis hijau, dan penguatan kolaborasi interdisipliner sangat penting untuk mengatasi hambatan skalabilitas serta mempersiapkan inovasi ini menuju aplikasi klinis.

Kata kunci: Fitokimia; Sistem penghantaran nano; Bioavailabilitas; Translasi klinis; Skala industri.

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Introduction

Plants are the primary source of bioactive phytochemicals, which offer vast opportunities for modern drug discovery [1]. Phytochemicals are a highly diverse group of bioactive compounds that include polyphenols, alkaloids, flavonoids, and terpenoids [2]. These molecules can selectively regulate cellular processes and have various beneficial properties, including antioxidant, anti-inflammatory, antihypertensive, and antiviral effects [1]. Clinically, compounds derived from natural sources have proven effective in treating various pathological conditions, including cancer, Alzheimer's disease, infections, and coronary heart disease. Currently, more than half of the new drugs being developed come from plants or are synthetic compounds that use phytochemicals as pharmacophores. However, limitations in conventional pharmaceutical formulations often hinder the clinical application of these bioactive compounds despite their therapeutic potential. Major obstacles include poor solubility, low stability, rapid metabolism, and low systemic bioavailability [3, 4].

In research on drug delivery systems, the Biopharmaceutics Classification System (BCS) is used to evaluate the profile of pharmaceutical active ingredients. More than 40% of plant-derived compounds have poor water solubility. This limits their absorption in the gastrointestinal tract, reducing systemic circulation levels and resulting in their classification as BCS Class II or Class IV. Specifically, this criterion indicates that the maximum single dose of the drug cannot completely dissolve in 250 mL of an aqueous solution [5, 6]. From a pharmacokinetic perspective, solubility and permeability are the primary parameters that determine successful in vivo absorption [7]. For a compound to be optimally absorbed, it must first be in a soluble form at the absorption site. Therefore, substances with low solubility face significant barriers when crossing the gastrointestinal epithelium. This drastically limits the fraction of the drug that enters systemic circulation, resulting in low oral bioavailability and making it difficult to achieve effective therapeutic concentrations via conventional routes of administration [6, 7].

To address the low solubility and dissolution rates of hydrophobic compounds, nanoscale delivery systems offer a highly rational solution. Through nanotechnology engineering and the use of specific excipients, these systems encapsulate therapeutic drugs to enhance solubility and physicochemical stability. Furthermore, this approach enables control over drug release rates, facilitates accumulation at specific target sites, and significantly reduces systemic toxicity [8, 9]. To date, various nano-carrier architectures have been extensively developed, including polymeric nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, niosomes, dendrimers, and micelles. These nano-platforms offer complete protection against phytochemical degradation and guarantee an ideal release profile of bioactive compounds, thereby directly improving absorption rates and therapeutic effectiveness [10]. Although the research landscape at the laboratory level is highly promising, the clinical translation of these technologies often faces roadblocks. Therefore, this narrative review aims to critically evaluate the application of nano-delivery systems for hydrophobic phytochemicals, with a particular focus on identifying translation barriers and challenges in industrial-scale upscaling. This analysis is expected to bridge the essential gap between fundamental innovations in the laboratory and their practical applications in the pharmaceutical industry.

Characteristics of Physicochemical and Biopharmaceutical Barriers

Structural Characteristics

One of the clinical limitations that hinders the application of phytochemicals in clinical settings is their low water solubility, which stems from their intrinsic structural characteristics. The physicochemical properties of these molecules directly impact their processing, delivery, and therapeutic performance. These

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characteristics influence how drugs interact with biological systems, affecting solubility, permeability, and the overall pharmacokinetic profile [11]. These bioactive molecules generally have rigid, aromatic, polycyclic carbon frameworks and a limited distribution of polar groups, such as hydroxyl or carboxyl. Consequently, thermodynamic interactions between phytochemical and water molecules become unfavorable, preventing spontaneous dissolution in physiological fluids [12].

The presence of carbonyl and phenolic hydroxyl groups in the flavonoid class allows for the formation of extensive intra- and intermolecular hydrogen bonding networks. Combined with π-π interactions between aromatic rings that result in a planar conformation, these molecules are packed so tightly that they resist penetration by aqueous solvents due to thermodynamic properties. In contrast, the hydrophobic nature of terpenoids is driven primarily by their highly abundant lipophilic alicyclic carbon framework, resulting in very low aqueous solubility. Meanwhile, alkaloids, which are nitrogen-containing organic bases in their free base form, often have poor water solubility due to the dominance of strongly hydrophobic structures, such as phenyl ring cores and isoquinoline frameworks. Phenolic acids are characterized by multiple phenolic hydroxyl group substitutions on the benzene ring. They have limited solubility due to their tendency to form rigid dimers, and they are highly susceptible to chemical instability and photosensitivit [13].

Absorption and Metabolism Barriers

In accordance with the assertions put forth by Bhalani et al. (2022), structural hydrophobicity has been identified as the rate-limiting step in drug absorption in the gastrointestinal tract [7]. Phytochemical molecules that cross the intestinal epithelium encounter solubility barriers and undergo extensive first-pass metabolism. The liver, a primary metabolic organ, significantly restricts the oral bioavailability of phytochemical compounds by extracting them, in addition to its role in the intestine. Phases I and II, which are mediated by cytochrome P450 and UDP-glucuronosyltransferase (UGT) (EC 2.4.1.17), respectively, rapidly convert the free molecules into inactive, water-soluble metabolites that can easily be excreted. These pathways account for over 80% of metabolism in the intestine and liver. Consequently, the fraction of intact drug that successfully reaches the systemic circulation decreases drastically due to a combination of slow dissolution and extensive enzymatic degradation [14, 15].

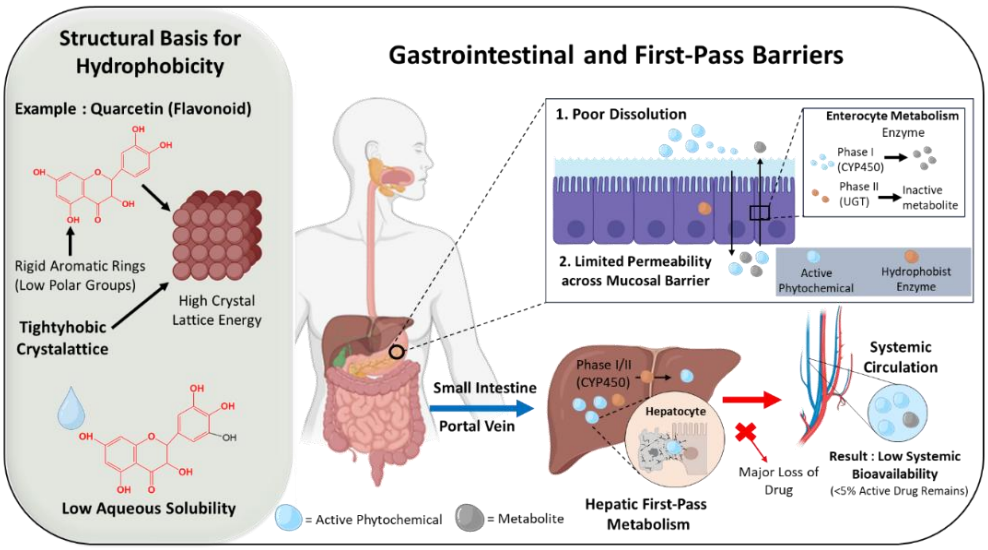

Figure 1. Schematic representation of the biopharmaceutical barriers limiting the oral bioavailability of phytochemicals.

As a prime example, the flavonoid class is known to have a very low bioavailability profile due to aggressive phase II metabolism, which refers to the body's process of modifying substances for easier elimination. These compounds are prone to sulfation, methylation, and glucuronidation in the upper gastrointestinal tract and the liver; consequently, following consumption, these molecules are predominantly present in their conjugated forms in blood plasma. Furthermore, the absorption kinetics of flavonoids are highly dependent on their molecular weight; the larger the molecule, the more difficult it is for it to penetrate membranes [16]. Structural modifications, such as the type of sugar group (saccharide moiety) attached, also significantly influence the rate of absorption. For example, the bioavailability of quercetin glycosides derived

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from apples reaches only 30% compared to quercetin glycosides from onions. This happens because the small intestine quickly absorbs quercetin glucoside, which causes a high peak plasma concentration. On the other hand, the large intestine only absorbs its rutinoside form after gut microbiota breaks it down. This translational challenge is further compounded by post-absorption metabolic conversion, where the primary forms of quercetin detected in systemic circulation are sulfated or methylated conjugates, rather than the aglycone or intact glycoside molecules [17, 18]. Furthermore, curcumin, the active compound in turmeric, is rapidly metabolized and excreted, resulting in suboptimal concentrations due to pharmacokinetic limitations. Its low water solubility and rapid metabolism further limit its clinical use [19].

Current Strategies In Nanoformulation

Nanotechnology-based drug delivery systems have been extensively developed to address the biopharmaceutical limitations of phytochemicals. These limitations include low water solubility, efflux by P-glycoprotein (P-gp), and extensive first-pass metabolism. Modifications at the nanoscale have been shown to improve solubility, stability, and absorption, as well as facilitate targeted delivery. This approach offers technical advantages, including protection from enzymatic degradation, controlled release profiles, and preferential accumulation in target tissues. The combination of these factors maximizes therapeutic effects while minimizing systemic side effects [20].

Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs)

Lipid-based nanoparticles (LNPs), particularly SLNs and NLCs, are the primary choice for delivering bioactive compounds. LNPs offer a stable and biocompatible lipid matrix, protecting the active ingredient from degradation caused by light, humidity, gastric acid conditions, and enzymatic activity [21]. These systems significantly enhance the solubility and oral bioavailability of water-insoluble phytochemical compounds. LNPs facilitate lymphatic absorption, allowing the drug to bypass first-pass metabolism in the liver [22]. Thanks to their encapsulation efficiency, SLNs and NLCs are ideal for delivering a broad spectrum of compounds, ranging from lipophilic groups (such as carotenoids) and compounds with low solubility (such as curcumin and quercetin) to hydrophilic compounds [23].

As a first-generation LNP, SLNs consist of lipids that are solid at room temperature, with particle sizes ranging from 30 to 1,000 nm [24]. The primary advantage of SLNs with sizes of 120–200 nm is their ability to avoid filtration by the spleen and liver (Ganesan et al., 2018). Good industrial scalability and ease of formulation without toxic organic solvents make them relevant for clinical applications [25]. To optimize oral delivery, SLNs are often surface-modified with mucoadhesive polymers such as chitosan. This coating prevents premature release in the stomach and enhances interaction with the intestinal mucosa [22]. For example, chitosan-coated SLNs loaded with Aloe perryi extract demonstrated significant anticancer efficacy against various cancer cell lines, proving their potential as a robust delivery system [26].

NLCs were developed as a second-generation formulation that overcomes the load capacity limitations of SLNs. NLCs are produced by combining a binary mixture of solid and liquid lipids to form an amorphous matrix. This structural imperfection creates more space for active molecules and prevents drug leakage during storage [27, 28]. NLCs are administered orally, where their lipid components trigger the formation of chylomicrons that facilitate drug transport via the lymphatic pathway. NLCs also facilitate the absorption of nutrients by intestinal cells and expedite the movement of nutrients through these cells. Additionally, NLCs inhibit the activity of the drug-rejecting P-glycoprotein (P-gp) enzyme. They are small, which means they have more surface area. This also means they stay in the stomach longer and interact more with the mucosal surface, which helps them be absorbed better [22].

Liposomes and Phospholipid Vesicles (Phytosomes)

Liposomes are nano-scale enclosed vesicles (ranging in size from 50 to several hundred nanometers) composed of one or more phospholipid bilayers surrounding an aqueous compartment[29]. This amphiphilic structure provides excellent biocompatibility for encapsulating various phytochemicals, whether hydrophilic within the aqueous core or hydrophobic at the lipid bilayer interface [30]. The structural flexibility of liposomes allows for diverse administration routes, including oral, topical, and parenteral, while protecting sensitive compounds such as polyphenols and carotenoids from physiological degradation [31]. As a targeted delivery system, liposomes significantly stabilize therapeutic compounds, overcome cellular absorption barriers, and optimize drug biodistribution in vivo [32]. Due to these advantages, this technology has been

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widely and successfully applied in various therapeutic modalities, including cancer therapy, antibiotics, antifungals, and vaccination [33]

Phytosomes range in size from 50 to 10,000 nm. They are a specific vesicular innovation. They are designed to enhance the absorption and bioavailability of poorly soluble phytochemicals. Unlike conventional liposomes, phytosomes form direct molecular complexes of active phytochemicals and phospholipids, such as phosphatidylcholine, via chemical bonds in an aprotic solvent. In this structure, the lipophilic phosphatidyl moiety acts as an outer shell surrounding the hydrophilic phytoconstituent-choline bond. This interaction results in significantly higher encapsulation efficiency and stability, enabling the use of lower doses of active compounds to achieve the desired biological effects [34]. When administered orally, phytosomes minimize degradation by digestive enzymes and gut microbiota while prolonging retention time in the small intestine to maximize absorption [35]. Various recent studies have demonstrated these systemic advantages. Encapsulating secondary metabolites, such as quercetin, curcumin, and berberine, in phytosomes has been shown to drastically improve their solubility and anticancer efficacy compared to their free extract forms [36].

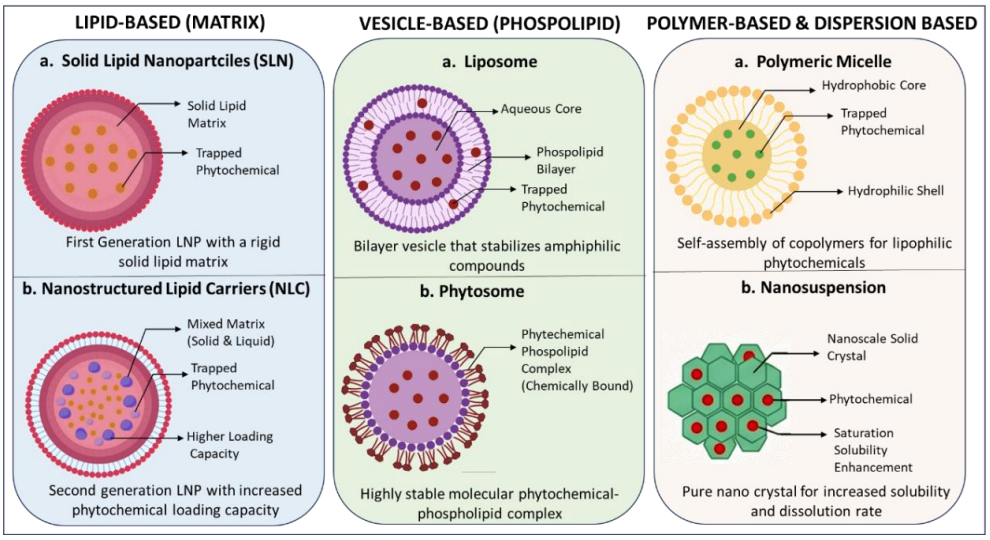

Figure 2. A schematic representation of current nanoformulation strategies for the delivery of phytochemicals.

Polymeric Micelles and Nanosuspensions

Polymeric micelles (PMs) are nanoscale delivery systems with a core-shell architecture. They form through the spontaneous self-assembly of amphiphilic copolymers. This assembly takes place in an aqueous environment [37]. Due to their high loading capacity, PMs can isolate hydrophobic compounds within their core. The hydrophilic shell can be modified with neutral segments or polyelectrolytes. These segments can be anionic, cationic, or zwitterionic. This modification provides structural protection. It also provides physicochemical flexibility. And it provides excellent in vivo biocompatibility [20]. PMs enhance the oral absorption of phytochemicals through four mechanisms: (1) protection of the drug from the harsh environment of the gastrointestinal tract, (2) controlled drug release, (3) prolonged retention time in the intestine via mucoadhesive properties, and (4) inhibition of cellular efflux pumps. PMs can also be engineered by grafting specific functional groups, such as pH-sensitive ligands or receptors, to direct drug release during the optimal absorption window in the gastrointestinal tract [38].

On the other hand, a nanosuspension is a colloidal dispersion of pure drug crystals at the nanoscale (with an average diameter of 200–500 nm) that is stabilized without the need for a polymeric carrier matrix [39]. This technology specifically addresses the limitations of phytochemicals and drugs classified as BCS Class II. By drastically reducing particle size, nanosuspensions exponentially increase the specific surface area, dissolution rate, and saturated solubility of the compound in the gastrointestinal fluid. The most significant therapeutic advantage of this enhanced in vivo dissolution is its ability to minimize the food effect. As a result, nanosuspensions can offer a stable and consistent oral bioavailability profile while effectively minimizing the absorption variability that frequently arises between fasting and postprandial states [40, 41].

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Table 1. A comparison of structural characteristics, mechanisms for enhancing oral bioavailability, and specific advantages of various nanoformulation strategies for the delivery of phytochemicals

Nano-Delivery System	Main Characteristics & Structure	Mechanisms for Increasing Bioavailability	Specific Advantages
Lipid Nanoparticles (SLN & NLC)	Nano-scale lipid matrix (30–1000 nm); SLNs have a rigid solid matrix, whereas NLCs have an irregular solid-liquid matrix.	Stimulates the formation of chylomicrons for absorption via the lymphatic route (bypassing first-pass hepatic metabolism); facilitates absorption via M cells.	High biocompatibility; protects compounds from stomach acid; NLC offers higher loading capacity without the risk of leakage.
Liposomes & Phytosomes	Phospholipid-based vesicles. Liposomes have a bilayer that surrounds an aqueous core; phytosomes form direct molecular complexes (chemical bonds) with phytochemicals.	Facilitates direct fusion with the cell membrane; prolongs retention time in the small intestine; minimizes degradation by enzymes and the microbiota.	Very high stability profile (especially phytosomes); improved dose efficiency; successfully applied via various routes of administration.
Polymeric Micelles (PM)	A core-shell structure formed by the self-assembly of amphiphilic copolymers in an aqueous environment.	Protecting drugs in extreme environments; inhibiting cellular efflux pumps (P-gp); delivering drugs precisely within the absorption window.	High loading capacity for hydrophobic compounds; the shell can be engineered with mucoadhesive polymers or pH-sensitive/receptor-binding ligands.
Nanosuspension	A colloidal dispersion of pure drug crystals (200–500 nm) without a polymeric carrier matrix.	Extreme particle size reduction results in an exponential increase in specific surface area, dissolution rate, and solubility at saturation.	Highly effective for Class II BCS drugs; minimizes the food effect; provides a stable and consistent oral absorption profile.

Quantitative Evaluation of Phytochemical Pharmacokinetic Enhancement

Although various nanoformulation systems have demonstrated theoretical and mechanistic advantages, proving their clinical efficacy requires comprehensive, quantitative evaluation. In vivo pharmacokinetic parameters, such as increases in area under the curve (AUC), maximum plasma concentration (Cmax), and bioavailability ratio, serve as key indicators for comparing the relative performance of each delivery system. Table 2, for example, presents quantitative comparative data for several model phytochemical compounds (such as curcumin and quercetin) formulated into various nanoarchitectures. This comparison provides an objective picture of each system's ability to enhance drug absorption compared to its free drug suspension.

Pharmacokinetic, Safety, and Toxicological Profile

Improvement of the ADME Profile (Absorption, Distribution, Metabolism, and Excretion)

In recent decades, absorption, distribution, metabolism, and excretion (ADME) properties have often been the primary factors contributing to the failure of bioactive compounds as new drug candidates [56]. Encapsulating phytochemical compounds into nanocarriers fundamentally alters their classical pharmacokinetic profiles, resulting in significant improvements in ADME parameters. Nanocarriers can be engineered to provide zero-order or sustained release kinetics by manipulating polymer composition, particle size, surface chemistry, and encapsulation efficiency [31].

During the absorption phase, the carrier's nanoscale size and surface modifications facilitate absorption via paracellular and transcellular routes. Unlike most oral drugs, which are transported via the systemic portal vein, this system activates intestinal lymphatic transport, which is ideal for lipophilic compounds. This lymphatic pathway offers three crucial advantages: (i) it avoids first-pass metabolism in the liver, (ii) it prolongs the duration of drug transport, and (iii) it unlocks the potential for direct drug targeting to the lymph, which is highly relevant for the treatment of lymphatic cancers as well as infections such as leishmaniasis and AIDS [57].

Nanoencapsulation keeps bioactive compounds in the body longer, which is important for distribution. Understanding these patterns is crucial for tailoring drug release profiles to meet specific therapeutic needs

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[22]. Surface modification with hydrophilic polymers, such as polyethylene glycol (PEG), prevents opsonization by the reticuloendothelial system (RES). This allows the drug to accumulate more in target tissues [58]. For instance, a biodistribution study in rats revealed that curcumin formulated in PLGA-PEG-PLGA micelles reduced liver and spleen uptake while enhancing distribution to target organs, including the lungs and brain [59].

During metabolism, the nanomaterial matrix acts as a steric shield, safeguarding phytochemicals from premature degradation. This degradation is caused by digestive enzymes in the intestinal lumen and cytochrome P450 enzymes in the liver. By bypassing the hepatic route, the formulation enhances targeting of the intestinal lymphatic area, thus improving absorption [60, 61]. In the excretion phase, the nanoformulation reduces the rapid renal clearance typically experienced by free, water-soluble phytochemical molecules, thereby prolonging the drug's biological half-life (t½) in the body [62].

Table 2. In Vivo Pharmacokinetic Profiles of Various Nanodelivery Systems for Model Phytochemical Compounds

Compounds	Nanoformulation System	Increase in Relative Pharmacokinetic Parameters	Animal Models	References
Curcumin	SLN	AUC increased 4.8-fold (relative bioavailability 480%); Cmax increased 4.48-fold.	Mice	[42]
	NLC	AUC increased 4.36-fold (relative bioavailability 436%); Cmax increased 3.41-fold.	Mice	[42]
	Phytosome (Phospholipid Complex)	Systemic absorption (total curcuminoids in the blood) increased up to 7.9-fold.	Healthy Human Volunteers	[43]
	Polymeric Micelles (MPEG-PCL)	AUC increased 52.8-fold; Cmax increased 7.51-fold; elimination half-life was longer.	Rats	[44]
	Nanosuspension (Phospholipid Complex)	Relative bioavailability (based on AUC) reached 621.50% (~6.2-fold).	Rats	[45]
Berberine	SLN	Bioavailabilitas relatif (AUC) meningkat 2.8 kali lipat; Cmax meningkat ~2.8 kali lipat.	Rats	[46]
	Selenium-coated Nanostructured Lipid Carriers (SeNLCs)	Relative oral bioavailability increased approximately 6.63-fold.	Sprague-Dawley rats	[47]
	Hyaluronic Acid-Based Liposomes	Relative bioavailability (AUC) increased 4.38-fold; Cmax increased approximately 3.15-fold.	Rats	[48]
	Solid Polymeric Particles (β-cyclodextrin)	Oral bioavailability increases by approximately 54% to 86% (1.54–1.86 times).	Rats	[49]
	Nanosuspension	The AUC increased 27.38-fold; Cmax increased 8.44-fold.	Wistar Rats	[50]
Resveratrol	SLN	Relative bioavailability (AUC) increased by approximately 1.21-fold.	Rats	[51]
	Folic acid-modified NLCs (FA-NLCs)	The AUC increased by up to ninefold.	Wistar Rats	[52]
	Cationic Liposomes	AUC increased 3.2-fold; Cmax increased 2.2-fold	Rats	[53]
	Mixed Polymeric Micelles Based on Lecithin (saLMPMs)	Absolute bioavailability increased 2.17-fold when administered orally	Rats	[54]
	Nanosuspension	Relative bioavailability (AUC) increased approximately 1.6-fold; Cmax increased approximately 5.7-fold.	Rats	[55]

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Safety and biocompatibility evaluation of nanotechnology excipients

Nanostructured systems have been demonstrated to offer significant improvements in therapeutic efficacy for various biomedical applications. However, it is imperative to acknowledge that the utilization of nanoscale materials also necessitates a comprehensive understanding of their potential health and safety risks. Thus, the choice of raw materials (excipients) for a matrix is a key factor in making sure that a formulation is safe for use in clinical settings [63]. Most modern nanoformulations, like SLNs, NLCs, and liposomes, are made up of physiological lipids, such as triglycerides and phospholipids. These lipids are very biocompatible because the body can break them down through its own lipid metabolic pathways. These materials have been approved by the Food and Drug Administration (FDA) and are classified as Generally Recognized as Safe (GRAS) [64, 65]. During the formulation process, the selection of solid and liquid lipids must be carefully evaluated. For example, the homogeneity and macroscopic phase separation of lipids below their melting points can be observed. The selected excipients must not only be biocompatible and stable under environmental conditions but also possess sufficient capacity to dissolve, encapsulate, or integrate various drug molecules onto the particle surface or within the aqueous phase [66]. Conversely, for polymeric micelles, the utilization of biodegradable polymers, such as chitosan or PLGA (poly(lactic-co-glycolic acid)) copolymers, ensures that degradation byproducts (e.g., lactic acid and glycolic acid) can be safely eliminated via the citric acid cycle [67]. Additionally, the evaluation of surface charge, otherwise known as zeta potential, is of significance. Nanoparticles that possess excessively high cationic charges are frequently subjected to rigorous evaluation due to their capacity to compromise cell membrane integrity through excessive electrostatic interactions [68].

In vitro and in vivo toxicological profiles

The toxicity of nanomaterials can result from diverse mechanisms, including oxidative stress, inflammation, genotoxicity, and various forms of cell death (i.e., apoptosis, autophagy, and necrosis). Clinically, this toxicity is classified into two distinct categories: acute toxicity, which involves tissue damage or inflammation that occurs immediately after exposure, and chronic toxicity, which refers to long-term effects such as organ damage or carcinogenesis. Consequently, conducting exhaustive in vitro and in vivo toxicological evaluations is imperative to ascertain the therapeutic window of a delivery system [69]. In vitro assessment is an absolute prerequisite (de facto) for identifying potential acute hazards and determining the minimum toxic dose. Preliminary findings from cell viability assays, including the MTT assay, generally indicate that lipid-based and natural polymer-based nanoformulations exhibit adequate biocompatibility and do not induce significant toxicity in healthy cells, even at high concentrations. Furthermore, parameters such as the level of reactive oxygen species (ROS) formation and the potential for apoptosis induction in non-target cells are evaluated to screen for toxicity mechanisms before proceeding to the animal preclinical stage [70].

While in vitro testing is essential, this method falls short in tracking systemic biodistribution and bioaccumulation pathways, highlighting the continued need for in vivo evaluation. Preclinical evaluations are generally conducted following the principles of Good Laboratory Practice (GLP) standards, which include assessing the maximum tolerated dose (MTD) and the maximum feasible dose (MFD). Moreover, these evaluations involve conducting acute and chronic toxicity tests using both rodent and non-rodent animal models [71]. Biodistribution and clearance studies employ animal models, such as mice and rats, to monitor the accumulation, tissue localization, persistence, and metabolic fate of nanoparticles. Systemic toxicity indicators are assessed through changes in serum biochemical parameters, blood cell profiles, and histopathological examinations. Numerous analyses of organ function biomarkers (e.g., aspartate aminotransferase [AST], alanine aminotransferase [ALT], and creatinine) have been performed to determine the safety profile of therapeutic doses of nano-encapsulated phytochemicals, including alkaloids like berberine. The results of these analyses have confirmed that such doses do not cause tissue necrosis, systemic inflammation, or immunotoxicity [72, 73].

Specific Therapeutic Applications

Cancer: Targeted Delivery to the Tumor Microenvironment

One of the greatest challenges in oncology is delivering phytochemical compounds specifically to their primary target: the tumor microenvironment (TME). The TME is a dynamic and complex network that plays a crucial role in the initiation, progression, and therapeutic resistance of cancer. By targeting the unique characteristics of the TME, nano-delivery systems can be designed to penetrate the dense extracellular matrix (ECM), bypass efflux pumps, and specifically reach tumor cells. Furthermore, by integrating stimulus-

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responsive materials, nanoformulations can release their therapeutic payload upon exposure to local environmental signals such as acidic pH variations, hypoxia, or the presence of specific enzymes, thereby significantly enhancing drug efficacy and reducing toxicity (Hoang et al., 2025; Shao et al., 2025).

As a prospective delivery system for pharmaceutical agents, Nano-DDS boasts three fundamental mechanistic advantages. These advantages pertain to the targeting of the tumor microenvironment (TME) and the overcoming of multidrug resistance (MDR). First, active targeting: Nano-DDS can be designed to carry specific ligands or antibodies on its surface, thereby enhancing recognition and direct binding to tumor cells. Secondly, the release must be slow and controlled. This system has been demonstrated to regulate the rate of drug release, thereby reducing the frequency of administration and minimizing side effects. Moreover, it has been shown to maintain effective concentrations at the tumor site. Thirdly, optimal penetration: By modifying the dimensions and optimizing the configuration, nanoformulations can diminish the friction barriers that exist between them and the surrounding environment while concurrently augmenting their affinity for target cells. This augmentation in affinity results in a substantial enhancement in the penetration of the physical barriers of the TME [74].

The proposed formulations have been shown to offer several theoretical advantages, as evidenced by various modifications (see Table 3 for a summary). For instance, Solid Lipid Nanoparticles (SLNs) produced via organic solvent-free coacervation have been demonstrated to facilitate a toxicologically safer release of quercetin, as evidenced by research conducted by Talarico et al. in 2021. In the context of direct targeting, the cationic SLNs were administered in a mucoadhesive in situ gel to treat bladder cancer (intravesical therapy), effectively preventing the excretion of the drug in urine [75]. An alternative localized strategy involves the administration of resveratrol liposomes in a buccal film formulation for the chemoprevention of oral cancer. This approach was first described by de Jesús Valle et al. in 2024. Conversely, chitosan-based polymer nanoparticles have the capacity to facilitate the delivery of small molecules. For instance, folate-modified chitosan nanoparticles have been shown to expedite the release of curcumin under acidic conditions (TME pH) by virtue of the protonation of amino groups. This phenomenon results in enhanced therapeutic efficacy against breast cancer cells without any deleterious effects on healthy cells [76]. Finally, the modification of drug formulations via nanosuspensions using the anti-solvent technique has been demonstrated to markedly enhance the dissolution rate of betulinic acid, thereby directly augmenting its antitumor efficacy [77].

Neurodegenerative Diseases: Blood-Brain Barrier Penetration

The blood-brain barrier (BBB) plays a crucial role in protecting the central nervous system (CNS). The primary functions of the BBB include supplying nutrients to the brain, maintaining ionic balance to preserve brain integrity, and blocking the entry of macromolecules, neurotoxins, and toxic chemicals from the bloodstream [78]. On the other hand, this strict selectivity poses a major barrier to the transfer of most drugs—both small molecules and macromolecules such as peptides and proteins—thereby severely limiting the effectiveness of CNS disease therapies, including those for neurodegenerative diseases, brain tumors, and stroke [79].

To overcome these anatomical barriers, nano-delivery systems (nano-DDS) such as nanosuspensions, liposomes, phytosomes, and lipid nanoparticles offer breakthrough strategies for effectively crossing the BBB to reach target cells such as neurons, microglia, and astrocytes. Based on its formulation matrix, phytosome technology addresses this issue by complexing the active compound with phospholipids. Curcumin phytosome formulations, for example, have been shown to enhance bioavailability, thereby penetrating the brain and acting as a potent anti-inflammatory agent by suppressing chronic glial cell activation in models of neurodegenerative pathology [80]. Another advanced modification was demonstrated by Noor et al. (2022), who designed red blood cell membrane-coated polymeric nanoparticles (RPCNPs) loaded with curcumin and the T807 ligand. This formulation demonstrated significantly increased BBB penetration and exhibited high affinity for hyperphosphorylated tau protein, thereby inhibiting a key pathway in Alzheimer's disease pathogenesis [81].

The use of NLCs has also shown very promising results. For example, Meng et al. (2015) encapsulated curcumin in NLCs to enhance its accumulation in the brain; pharmacokinetic studies demonstrated that curcumin levels in the subjects' brains were significantly higher compared to the administration of free curcumin without compromising its antioxidant activity. This NLC targeting strategy can even be made more specific [82]. Pinheiro et al. (2020) functionalized NLCs with the RVG29 peptide and loaded them with quercetin to target nicotinic acetylcholine receptors in the brain. As a result, the permeability of these

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nanoparticles through an in vitro BBB model increased dramatically by up to 1.5-fold compared to nanoparticles without the peptide modification [83].

Metabolic and Infectious Diseases: Enhanced Oral Bioavailability and Local Therapy

In cases of metabolic diseases and infections, the main challenge with oral drug administration often lies in its very low bioavailability. Metabolic syndrome (MetS), for example, is a cluster of medical conditions such as insulin resistance, central obesity, hypertension, and atherogenic dyslipidemia that significantly increase the risk of cardiovascular disease. To address the complexity of MetS and effectively treat infections, the modification of phytochemical compounds using nano-delivery systems (Nano-DDS) is essential to protect drugs from enzymatic degradation and enhance their absorption in the gastrointestinal tract [84].

In the field of metabolic diseases, nanoformulations have been shown to optimize the efficacy of antidiabetic compounds. For example, SLNs loaded with berberine (BBR) exhibit significantly better bioavailability compared to free BBR; oral administration of BBR-SLNs significantly reduces weight gain, improves insulin resistance homeostasis, and lowers fasting blood glucose levels [85]. Similar potential has also been observed in naringenin, a citrus flavanone compound with strong antihyperglycemic activity, which unfortunately is poorly water-soluble and rapidly eliminated by liver and intestinal enzymes [84]. To overcome these limitations, the use of chitosan/alginate core-shell nanoparticles impregnated with naringenin has been shown to be safe and to provide remarkable antidiabetic effects in mouse models, paving the way for more precise targeting of the large intestine [86].

In addition to treating metabolic diseases, innovations in nano-DDS are crucial for treating infections and protecting the gastrointestinal system. To protect phytochemicals from stomach acid, for example, curcumin polymeric micelles are encapsulated within an Eudragit S-100 matrix (a pH-sensitive polymer), ensuring targeted, maximal drug release in the intestine [87]. Oral absorption is also enhanced by nanostructured lipid carriers (NLCs), which increase the absorption of khellin molecules through the intestinal membrane [88], and by microfluidic-based curcumin nanosuspensions, which optimize particle size [45]. To ensure product stability, apigenin liposomes are coated with chitosan and converted into a solid powder via spray drying to enable controlled release in the gastrointestinal tract [89]. Berberine NLCs are highly effective in treating localized inflammation and infections by targeting colon tissue in patients with ulcerative colitis [90], while chitosan-modified gingerol phytosomes combat respiratory tract infections due to their strong mucoadhesive properties [91].

Challenges in Clinical Translation and Industrial-Scale Implementation

Challenges in scaling up production

Although phytochemical-based nanodelivery systems have gained tremendous popularity due to their ability to enhance solubility and oral bioavailability and protect drugs from degradation in the gastrointestinal tract [62], the transition from the laboratory to the industrial scale presents significant technical and financial challenges. The development of nano-carrier systems requires extensive optimization and entails high production costs. One of the main obstacles to this scalability is inter-batch variability. Since the composition and quality of plant extract compounds can naturally vary, maintaining consistent reproducibility and physicochemical properties of nanocarriers such as particle size, shape, surface modification, and long-term stability becomes highly challenging [95, 96]. Technical difficulties in maintaining product consistency directly lead to complexities in regulatory and safety aspects. The integration of nanotechnology with phytochemistry lies at the intersection of two distinct regulatory frameworks. Regulatory barriers become increasingly significant due to the lack of standardized protocols for testing the safety and toxicity of nanomaterials [95]. Therefore, a comprehensive assessment of the long-term toxicity of nanocarriers is crucial to ensure the safety of their clinical applications, particularly in long-term therapies such as cancer treatment [96].

To tackle the challenges of high production costs and scalability, enhancing manufacturing efficiency and embracing innovative design are essential. The initial critical step involves establishing standardized procedures for the extraction and purification of phytochemical raw materials, which ensures reproducibility. From a design point of view, technology can be improved by using co-loading strategies and sequential release mechanisms, like pH-sensitive polymers, to get the best results [96]. In terms of cost efficiency in manufacturing, adopting “green synthesis” methods or plant-mediated biosynthesis presents a viable alternative. These environmentally friendly approaches significantly decrease reliance on costly chemical reagents and energy-intensive processes, leading to the production of nanoparticles that are safer from a toxicological perspective and more cost-effective for large-scale production [4, 96].

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Table 3. Summary of Innovations in Nano-Delivery Systems for Various Phytochemical Compounds

Nano Delivery System	Phytochemical Compounds	Applications / Key Focus	Mechanisms & Outcomes	Ref.
Polymeric Micelles (Sustainable Production & pH-Sensitive Matrix)	Curcumin	Industrial Scale Efficiency & Synergistic Oral Delivery	1. Continuous Production: Utilizing coaxial turbulent jet technology to produce micelles (MPEG-PCL) with uniform size, optimal drug loading, and a sustained-release profile. 2. Matrix Encapsulation: Curcumin micelles are encapsulated within an Eudragit S-100 matrix (a pH-sensitive polymer) to protect the micelle structure from degradation by stomach acid, allowing the drug to be released in a targeted and maximized manner in the intestine.	[87, 92]
SLN (Coacervation Method & Mucosal Adhesive Gel)	Quercetin	Safety of Local (Intravesical) Administration	1. Coacervation Method: Production of organic solvent-free SLNs to encapsulate quercetin, resulting in a controlled-release profile that is safer from a toxicological perspective. 2. Mucosal Adhesive In Situ Gel: Cationic SLN is incorporated into a mucosal adhesive gel for direct (intravesical) treatment of bladder cancer, preventing rapid drug loss and enhancing cellular uptake.	[75, 93]
Liposomes (Buccal Formulation & Spray Drying)	Resveratrol, Apigenin	Local Delivery (Oral Mucosa) & Product Stability	1. Buccal Formulation: Resveratrol liposomes are incorporated into hydrogels and buccal films for the chemoprevention of oral cancer, ensuring prolonged drug retention at the site of mucosal lesions. 2. Chitosan Coating & Spray Drying: Apigenin liposomes are stabilized with a chitosan coating and converted into a solid powder, resulting in high storage stability and controlled release in the gastrointestinal tract.	[89, 94]
NLC	Berberine, Khellin	Improved Oral Bioavailability & Local Inflammation Therapy	1. Ulcerative Colitis Therapy: NLCs contain berberine to enhance oral absorption and provide significantly better anti-inflammatory effects on inflamed colon tissue. 2. Khellin Absorption: The use of NLCs drastically improves the solubility profile and oral absorption of khellin through the intestinal membrane compared to its free form.	[88, 90]
Nanosuspensions (Anti-Solvent Technique & Microfluidic Systems)	Betulinic Acid, Curcumin	Increased Dissolution Rate & High Oral Bioavailability	1. Anti-Solvent Technique: The preparation of nanosuspensions drastically increases the dissolution rate of betulinic acid and directly enhances its antitumor activity. 2. Microfluidic System: The preparation of curcumin-phospholipid nanosuspensions using microfluidics yields highly precise particle sizes, optimizing their physicochemical properties and oral absorption.	[45, 77]
Phytosome (Chitosan Complex & Anti-Inflammatory Formulation)	Gingerol, Curcumin	Treatment of Respiratory Infections & Anti-Inflammatory Agents for the Brain	1. Phytosome-Chitosan Complex: Gingerol phytosomes complexed with chitosan polymers have been shown in vitro and in vivo to enhance drug delivery for the effective treatment of respiratory tract infections. 2. Curcumin Phytosome: The phytosome formulation enhances the bioavailability of curcumin, allowing it to reach the brain and act as an anti-inflammatory agent against chronic glial cell activation, opening up significant potential for neurodegenerative therapy.	[80, 91]

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Standardization and Quality Control of Botanical Raw Materials

Although the global use of herbal medicines is growing exponentially, their quality, safety, and efficacy remain major challenges due to the lack of strict regulatory controls. Herbal medicines typically utilise plant matrices with highly complex constituents, many of whose active compounds have not yet been definitively identified. Therefore, the greatest inherent obstacle in the development of high-quality herbal nanomedicine products is the variability in phytochemical composition. External factors such as geographic location, climatic conditions, harvest season, and extraction methods heavily influence this variability. Extraction, as the initial step, is crucial for isolating the desired phytoconstituents, as it directly affects the yield, purity, and pharmacological integrity of the final product [97, 98]. The multicomponent nature of these plant extracts presents unique challenges, not only in formulation but also in the protection of intellectual property rights (IPR). Unlike single-molecule synthetic drugs, it is very difficult to claim ownership over the varying composition of extracts, so the industry often relies more on process patents or delivery systems. On the other hand, some formulations based on liposomes, polymers, and solid lipid nanoparticles have entered the market (such as liposomal curcumin and resveratrol), which are generally marketed as dietary supplements with claims of increased bioavailability. However, only a few nanopharmaceuticals have successfully achieved full pharmaceutical regulatory approval. This is due to strict safety requirements, monitoring of nanocarrier degradation, and demands for predictability in drug release kinetics. To address these complex standardisation challenges, a chromatographic fingerprinting approach using high-resolution instruments, such as High-Performance Liquid Chromatography (HPLC) or Ultra-Performance Liquid Chromatography-Mass Spectrometry (UPLC-MS), is highly recommended as the gold standard [31, 99].

In the context of clinical translation and industrial-scale production, this raw material standardization strategy must be integrated into the quality-by-design (QbD) framework. Pharmaceutical product development following the QbD approach begins with defining the Quality Target Product Profile (QTPP), which outlines the ideal characteristics of the final product, including dosage form, route of administration, strength, and formulation stability. Through QbD, formulators are required to establish safe specification ranges (upper and lower limits) for botanical raw materials. Generally, industry guidelines stipulate that the concentration tolerance range for marker compounds must not deviate by more than ±10–15% from the target value. This is intended to ensure the stability of downstream processes. Neglecting quality control of these raw materials can lead to catastrophic manufacturing failures [100]. Finally, given the potential dominance of future nano-delivery systems containing plant bioactives, long-term studies are absolutely necessary. These evaluations are crucial for monitoring the cellular uptake of encapsulated bioactive materials and mitigating potential risks, such as subclinical chronic inflammation, organ toxicity, or metabolic disorders, which may not be detected in short-term testing [101].

Impact of Critical Process Parameters (CPPs) on Reproducibility

Identifying and controlling critical process parameters (CPPs) is necessary to address inter-batch variability during production scale-up. CPPs are process-related parameters that significantly impact the quality of the target product. Implementing QbD in pharmaceutical manufacturing is a key approach for ensuring the efficacy and safety of pharmaceutical products. Implementing QbD can create significant value and benefits. Nanopharmaceuticals, in particular, face many challenges related to structural stability and a lack of understanding of the manufacturing process. Each method of preparing nanoparticle delivery systems has specific process parameters that directly influence the critical quality attributes (CQAs) of the formulation, such as particle size, polydispersity index (PDI), encapsulation efficiency (EE), and physicochemical stability. Understanding and validating the relationship between CPPs and CQAs is essential for ensuring reproducibility when scaling up processes from laboratory to industrial levels [102, 103]. Table 4 provides a practical guide for the scale-up process by summarizing the main CPPs and their impacts for the three most commonly used production methods.

Long-term physicochemical stability of the formulation

In addition to the challenges of large-scale production, maintaining the long-term physicochemical stability of nanoformulations during storage is a critical hurdle before the product can enter the clinical trial phase. This stability consistency is highly dependent on the quality of the phytochemical inputs; variability in the composition of botanical compounds not only affects initial loading efficiency but can also compromise the stability and bioactivity of the particles over time [31]. Mechanistically, these stability issues vary significantly depending on the carrier matrix. In lipid-based systems such as Solid Lipid Nanoparticles (SLNs),

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the most common obstacle is the polymorphic transition of the lipid matrix. During storage, lipids tend to shift from a high-energy crystalline form (α) to a more stable conformation (β). This internal structural change causes a reduction in space within the lipid matrix, which ultimately triggers the expulsion of drug molecules from the particle [108]. Similarly, in vesicular systems such as liposomes or polymeric micelles, the presence of an aqueous medium poses risks of drug leakage, lipid hydrolysis, and oxidation. To address this aqueous degradation, formulators typically employ further processes such as freeze-drying to convert liquid formulations into much more stable solid powders [109, 110]. Given this complexity, ongoing research integrating nanotechnology, chemistry, biology, and materials science is crucial for creating nanocarrier designs that are not only long-term stable but also exhibit high therapeutic efficacy with minimal toxicity [95].

Comprehensive characterization of these instability mechanisms requires evaluation using standard analytical methods. Differential scanning calorimetry (DSC) analysis routinely measures thermodynamic properties of thermally induced transitions. It has been applied to various biological macromolecules, such as lipids or proteins, which transition from an unstable to a more stable form during storage [111, 112]. X-ray diffraction (XRD) is employed as a complement to monitor real-time changes in crystalline phases, such as the transition from a metastable phase (highly soluble) to a stable phase (lowly soluble), or to identify specific alterations in the crystal lattice of the carrier matrix that may trigger drug expulsion [113]. Meanwhile, Fourier transform infrared spectroscopy (FTIR) plays a crucial role in measuring the interaction of infrared radiation with molecular bonds. This provides information about the biochemical compounds in the sample. FTIR can detect the presence or absence of chemical degradation, such as hydrolysis or oxidation. It can also monitor changes in functional bond interactions between phytochemical compounds and polymer or lipid excipients. Various case studies in the literature indicate [114].

Translational Gaps: From Animal Models to Humans

The majority of the potential of phytomedicine reported to date is still based on simple in vitro systems or small animal models, which are often unable to accurately predict pharmacological profiles and toxicity in humans. Significant differences in metabolism, immune response, and disease pathology across species can lead to overestimation of therapeutic benefits or inaccurate risk assessments. Consequently, preclinical success often fails to translate into the clinical phase. This underscores the urgency of using more predictive models and standardizing evaluation criteria [115]. The translational potential of these drugs heavily depends on the identification of bioactive components, clarification of mechanisms of action, assurance of safety profiles, and appropriate formulation. For example, Picrorhiza kurroa has been shown to possess significant hepatoprotective effects due to its iridoid glycoside content, particularly picroside. Recent studies highlight the plant's antioxidant, anti-inflammatory, and hypolipidemic activities in the management of non-alcoholic fatty liver disease (NAFLD). However, its clinical efficacy is highly dependent on formulation standardization and dose optimization. The main challenge in extrapolating data lies in fundamental biological differences. For instance, the expression of cytochrome P450 (CYP450) isoenzymes and UDP-glucuronosyltransferase (UGT) enzymes in the livers and intestines of mice differs significantly from that in humans. Furthermore, the expression levels and substrate affinity of efflux transporters, such as P-glycoprotein (P-gp) on the apical membrane of rat enterocytes, often do not correspond to human physiological conditions. These discrepancies frequently lead to overly optimistic assessments of oral bioavailability and safety profiles during preclinical testing [116, 117].

To mitigate the risk of clinical failure, researchers recommend the use of more physiologically relevant animal models, such as pigs (porcine models). Pigs offer greater anatomical and physiological similarity to humans compared to rodents, particularly regarding organ size, gastric pH, intestinal transit time, and gut microbiome composition. In addition to large animal models, advances in microfluidic technology have introduced organ-on-a-chip systems, such as gut-on-a-chip and liver-on-a-chip. This technology is capable of replicating the three-dimensional structure and blood flow dynamics of human organs in vitro. Thus, organ-on-a-chip systems provide far more accurate predictions of nanocarrier absorption, metabolism, and toxicity without having to rely entirely on animal testing [118-120].

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Table 4. The Effect of Critical Process Parameters (CPPs) on Critical Quality Attributes (CQAs) in Various Nanoformulation Production Methods

Production Method (Nanoformulation System)	Critical Process Parameters (CPPs)	Typical Value Ranges	Impact on Critical Quality Attributes (CQAs)	References
High-Pressure Homogenization / HPH (SLN, NLC)	Homogenization pressure	500 - 1500 bar	High homogenization pressure can lead to a decrease in absolute values, and pressure that is too low results in large particle sizes, while excessive pressure can cause particle aggregation due to high kinetic energy.	[104]
	Cycles	3 - 5 cycles	The optimal number of cycles reduces PDI (uniform particle size distribution); excessive cycling can cause compound degradation and damage the lipid matrix.	[105]
	Process and cooling temperatures	5 - 10°C above the melting point of the lipid	Determining the polymorphic transition of lipid crystals, which directly affects drug-loading capacity and long-term stability. High temperatures can accelerate the degradation of nanoparticle systems.	[106]
Thin-Film Hydration (Liposomes, Phytosomes)	Rotary evaporation temperatur	20 - 60°C	Affects the thickness and uniformity of the lipid film; temperatures below the gel-liquid transition phase will prevent the formation of a good thin film.	[102]
	Rotational speed	100 - 200 rpm	Constant rotation ensures a large film surface area, accelerates the rate of hydration, and generates higher shear forces within the barrel, which promotes the formation of a homogeneous emulsion consisting of the drug, lipids, and surfactants.	[106]
	Time and method of hydration	1 - 2 h	It has a strong influence on vesicle size and liposome homogeneity; incomplete hydration leads to high inter-batch variability in particle size.	[102]
Nanoprecipitation (Polymeric Micelles)	Organic phase injection rate	0,5 - 2 mL/minute	The injection rate dramatically alters the supersaturation profile; a rate that is too fast leads to uncontrolled nucleation and heterogeneous particles.	[107]
	Organic phase to aqueous phase ratio	1:5 to 1:10	It has a strong influence on the solubility of phytochemical compounds and the self-assembly ability of polymers, and affects colloidal stability.	[107]
	Stirring speed	500 - 1500 rpm	Constant stirring facilitates rapid diffusion of the organic solvent into the aqueous phase, prevents coalescence, and produces nanoparticles (low PDI).	[107]

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Conclusion

Overall, the low water solubility and poor oral bioavailability of various phytochemical compounds continue to pose major challenges in the development of modern therapeutics. However, rapid advances in the engineering of drug delivery systems at the nanoscale, such as lipid nanoparticles, liposomes, and phytosomes, have provided transformative solutions. More than just improving drug solubility, these nanoscale modifications enable the precise delivery of active molecules to penetrate various stringent biological barriers. Evidence from the literature indicates that nanoformulations have proven effective at penetrating the dense matrix of the tumor microenvironment (TME) in cancer therapy, crossing the blood-brain barrier (BBB) in neurodegenerative diseases, and significantly protecting drugs from gastric acid degradation for the treatment of metabolic and infectious diseases.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this study.

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