ISSN: 3139-3683

JOURNAL OF HEALTH SYNAPSE (JHS)

Peer Reviewed Refereed Open Access International Multidisciplinary Journal

Publisher: Scientistic Era Private Limited
Journal Hompage: https://healthsynapse.org

# Nanotechnology-Based Delivery Systems for Quercetin and Curcumin: Formulation Strategies, Bioavailability Enhancement, Therapeutic Applications, and Translational Challenges

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**ARTICLE INFO**

**KEYWORDS:**
*quercetin; curcumin; nanotechnology; nanoparticles; liposomes; solid lipid nanoparticles; nanostructured lipid carriers; nanoemulsions; bioavailability; pharmacokinetics*

**ARTICLE HISTORY**
**Received Date:** 25 July 2026
**Revised Date:** 08 August 2026
**Accepted Date**: 18 August 2026
**Published Date:** 25 August 2026

**CITATION**
Patel, R., 2026 Nanotechnology-Based Delivery Systems for Quercetin and Curcumin: Formulation Strategies, Bioavailability Enhancement, Therapeutic Applications, and Translational Challenges. *Journal of Health Synapse (JHS), 1(3), 27-40. https://doi.org/10.67529/jhs.v1i3.3*

**A B S T R A C T**

Quercetin and curcumin are extensively investigated plant-derived polyphenolic bioactives with antioxidant, anti-inflammatory, anticancer, and cytoprotective activities, but their translation into reproducible therapeutic products is restricted by unfavorable biopharmaceutical properties. Quercetin is a flavonol with limited aqueous solubility, extensive intestinal and hepatic conjugation, and formulation-dependent absorption, whereas curcumin is a diarylheptanoid curcuminoid - not a flavonoid - characterized by very low water solubility, chemical instability, rapid metabolism, and low systemic exposure after conventional oral dosing. Nanotechnology-based delivery systems have therefore been explored to increase apparent solubility, protect the payload from degradation, improve mucosal transport and cellular uptake, prolong residence or circulation, and enable controlled or targeted release. This review critically compares nanocarriers developed for quercetin and curcumin, including polymeric nanoparticles, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, self-emulsifying systems, micelles, nanocrystals, nanosuspensions, chitosan-based systems, and selected hybrid platforms. Particular attention is given to formulation composition, manufacturing approaches, critical quality attributes, pharmacokinetic evidence, therapeutic applications, and the distinction between preclinical promise and demonstrated clinical benefit. Human pharmacokinetic studies show that formulation can substantially alter systemic exposure for both compounds; however, cross-study fold-changes are not directly comparable because dose, analytical treatment of conjugated metabolites, reference formulations, and study design differ. Translation is additionally limited by scale-up, batch reproducibility, nanocarrier safety, long-term stability, regulatory characterization, and oral-product contamination control. A quality-by-design framework linking material attributes and process parameters to particle size distribution, drug loading, release, stability, and in vivo performance is proposed as a more defensible route toward clinically relevant products. Overall, nanotechnology can address important delivery barriers for quercetin and curcumin, but improved bioavailability should be treated as an enabling pharmacokinetic outcome rather than proof of therapeutic efficacy.

**Abbreviations:** API, active pharmaceutical ingredient; AUC, area under the concentration-time curve; CQA, critical quality attribute; DLS, dynamic light scattering; EE, encapsulation efficiency; FDA, U.S. Food and Drug Administration; FTIR, Fourier-transform infrared spectroscopy; GI, gastrointestinal; GMP, good manufacturing practice; NLC, nanostructured lipid carrier; NP, nanoparticle; PDI, polydispersity index; PK, pharmacokinetics; PLGA, poly(lactic-co-glycolic acid); QbD, Quality by Design; SEM-EDS, scanning electron microscopy-energy dispersive X-ray spectroscopy; SLN, solid lipid nanoparticle; SNEDDS, self-nanoemulsifying drug delivery system; TEM, transmission electron microscopy.

## I. Introduction

Plant-derived polyphenols occupy an unusual position in contemporary drug-delivery research: they are chemically diverse, biologically pleiotropic, widely consumed, and often supported by large preclinical literatures, yet many exhibit physicochemical and pharmacokinetic properties that make conventional dosage forms inefficient. Nanotechnology-based drug delivery is attractive in this setting because nanoscale carriers can alter dissolution, protect labile molecules, change interfacial interactions with biological membranes, and modulate distribution or release without requiring modification of the parent bioactive [1,2]. The clinical history of nanomedicines also shows, however, that successful translation depends on much more than reducing particle size. Product composition, size distribution, surface properties, payload state, release behavior, manufacturing reproducibility, and route-specific safety all become part of the therapeutic product [3,4].

Quercetin and curcumin are useful comparative models because they share several formulation problems while differing in chemical class and disposition. Quercetin (3,3',4',5,7-pentahydroxyflavone) is a flavonol and therefore a member of the flavonoid family. It is present in many fruits and vegetables, usually as glycosides, and undergoes extensive intestinal and hepatic metabolism after ingestion [5-12]. Curcumin (diferuloylmethane) is the principal curcuminoid associated with Curcuma longa; chemically, it is a diarylheptanoid polyphenol rather than a flavonoid. Conventional curcumin is poorly water soluble, unstable under several aqueous conditions, and rapidly transformed to conjugated and reduced metabolites, which contributes to low circulating concentrations after oral administration [29-34]. The taxonomic distinction is important because a review entitled solely around 'flavonoids' would incorrectly classify curcumin. The broader category of plant-derived polyphenolic bioactives is therefore more accurate.

The central formulation question is not whether nanosystems can increase apparent solubility - this is well established for many hydrophobic compounds - but whether a given carrier produces a reproducible and clinically meaningful change in exposure, tissue delivery, or therapeutic index. Quercetin delivery research includes lipid nanocarriers, polymeric nanoparticles, chitosan systems, liposomes, nanocrystals, nanoemulsions, micelles, cyclodextrin-assisted systems, and hybrid formulations [5,6,13-28]. Curcumin has an even broader formulation literature spanning polymeric nanoparticles, liposomes, lipid nanoparticles, nanoemulsions, micelles, nanogels, dendrimers, nanocrystals, protein-based systems, and hybrid nanostructures [29-54]. Across both compounds, the most robust mechanistic rationale is improved solubilization and protection; evidence for active targeting and disease-specific therapeutic superiority is more heterogeneous.

This review therefore focuses on formulation science rather than simply cataloguing pharmacological effects. It compares the major nanocarrier classes, relates formulation choices to the distinct biopharmaceutical barriers of quercetin and curcumin, evaluates human and preclinical pharmacokinetic evidence, identifies critical characterization and manufacturing variables, and examines safety, regulatory, and contamination-control issues relevant to pharmaceutical translation. The aim is to distinguish credible formulation advances from claims that remain primarily preclinical and to identify development priorities that could make future quercetin and curcumin products more reproducible, interpretable, and clinically testable.

## 2. Scope and Literature Approach

This article is a structured narrative review rather than a systematic review or meta-analysis. Literature was identified through searches of peer-reviewed records indexed in SciSpace and PubMed-accessible sources, publisher databases, and reference-list screening, with emphasis on studies available through August 2026. Search concepts combined quercetin or curcumin with nanoparticle, liposome, solid lipid nanoparticle, nanostructured lipid carrier, nanoemulsion, self-emulsifying system, micelle, chitosan, PLGA, nanocrystal, nanosuspension, bioavailability, pharmacokinetics, clinical, toxicity, scale-up, and regulatory terms. Recent reviews were used to map the field, whereas primary formulation, pharmacokinetic, and human studies were prioritized for quantitative statements. Seminal pre-2015 studies were retained when they established mechanisms or benchmarked bioavailability. Because formulations, analytical methods, doses, and routes are highly heterogeneous, fold-increases in exposure are interpreted within individual studies and are not pooled across platforms.

## 3. Physicochemical and Biopharmaceutical Basis for Nanoformulation

Quercetin has multiple phenolic hydroxyl groups but remains poorly soluble in water in its aglycone form. Its gastrointestinal behavior is further complicated by the fact that dietary quercetin is commonly present as glycosides, and the attached sugar affects absorption. In a human crossover study, Graefe and colleagues showed that quercetin from glucoside-containing preparations was absorbed differently from rutin-type material and that circulating quercetin was predominantly detected as conjugated metabolites rather than free aglycone [11]. Broader reviews likewise emphasize rapid glucuronidation, sulfation, and methylation, as well as the influence of food matrix and intestinal metabolism [7,9,10]. Consequently, a

quercetin formulation can improve exposure through several non-equivalent mechanisms: increasing dissolution of the aglycone, maintaining a solubilized fraction in intestinal fluids, promoting interaction with the epithelium, altering residence time, or protecting material until it reaches a preferred absorption site.

Curcumin presents a related but more severe solubility problem. Its hydrophobic structure produces very low aqueous solubility, while degradation and extensive metabolic transformation reduce the amount of unchanged compound reaching systemic circulation [29-32]. These limitations have been recognized for decades, and strategies including piperine co-administration, phospholipid complexes, micronization, amorphous dispersions, micelles, nanoparticles, and lipid systems have been investigated [29,31,32,35-39]. A critical complication is analytical: studies may quantify free curcumin, total curcuminoids after deconjugation, or specific metabolites, so apparent bioavailability gains can reflect differences in what is being measured. Stohs and colleagues highlighted the need to interpret hydrolyzed and non-hydrolyzed plasma measurements carefully [32].

The two compounds also differ in the strength and interpretation of their pharmacology. Quercetin has plausible antioxidant and anti-inflammatory actions and interacts with multiple signaling pathways, but most disease-specific nanoformulation evidence remains in vitro or in animal models [8,10,25,26]. Curcumin has an exceptionally large mechanistic literature, yet Nelson and colleagues argued that chemical instability, aggregation, fluorescence, redox behavior, and other assay-interference mechanisms can complicate interpretation of some screening data [33]. Padmanaban and Nagaraj subsequently argued against treating these limitations as grounds to dismiss all biological evidence [34]. For formulation science, the appropriate conclusion is methodological: nanoformulation studies should verify chemical integrity, distinguish carrier effects from payload effects, use orthogonal assays where possible, and avoid equating enhanced uptake or cytotoxicity with established clinical efficacy.

Table 1 summarizes the formulation-relevant differences. Both molecules benefit from protection and solubilization, but quercetin development must pay particular attention to glycoside/aglycone form and conjugated metabolites, whereas curcumin development must additionally address chemical instability and the measurement of parent compound versus metabolites. These distinctions should guide both formulation design and the choice of pharmacokinetic endpoints.*[5-12,29-34]*

**Table 1. Comparative formulation-relevant properties of quercetin and curcumin.**

| **Attribute** | **Quercetin** | **Curcumin** | **Formulation implication** |
|---|---|---|---|
| Chemical class | Flavonol; flavonoid | Diarylheptanoid curcuminoid; polyphenol | Avoid classifying curcumin as a flavonoid; select analytical methods based on distinct chemistry. |
| Major barrier | Low aqueous solubility plus extensive intestinal/hepatic conjugation | Very low aqueous solubility, chemical instability, rapid conjugation/reduction and elimination | Both benefit from solubilization/protection; curcumin additionally requires stringent chemical-stability control. |
| Circulating species | Predominantly glucuronide, sulfate and methylated metabolites after oral intake | Parent often low; glucuronide/sulfate and reduced metabolites can predominate | PK studies should state whether free parent, deconjugated total, or individual metabolites are quantified. |
| Formulation-sensitive factors | Aglycone vs glycoside, food matrix, intestinal processing, carrier-mediated solubilization | Crystal state, degradation, dissolution, metabolic inhibition, carrier-mediated solubilization | Comparator formulation strongly affects reported fold-bioavailability. |
| Common nano-platforms | Polymeric/chitosan NPs, liposomes, SLNs/NLCs, nanoemulsions, micelles, nanocrystals, cochleates | Polymeric NPs, liposomes, SLNs/NLCs, nanoemulsions, micelles, nanocrystals, nanogels, hybrid/inorganic systems | Platform should be chosen for route and barrier, not novelty alone. |
| Key translational caution | Improved absorption does not establish | Assay interference/instability | Use orthogonal assays, chemically specific |

| | | | |
|---|---|---|---|
| | disease efficacy | can complicate mechanistic claims; exposure gain does not establish efficacy | analytics, blank-carrier controls, and clinically relevant endpoints. |

## 4. Nanotechnology Platforms: Design Principles Relevant to Both Compounds

Nanocarrier selection should begin with the intended route and target product profile rather than with the availability of a particular nanotechnology. Liposomes provide a phospholipid bilayer capable of accommodating hydrophobic payloads and can be surface-modified, but their performance depends strongly on lipid composition, lamellarity, oxidation control, leakage, and storage stability [56]. SLNs use a largely solid lipid matrix, while NLCs introduce liquid lipid or structural disorder to increase payload accommodation and reduce drug expulsion during storage [55]. Nanoemulsions are kinetically stable dispersions rather than thermodynamically stable microemulsions; their small droplets can maintain hydrophobic compounds in a solubilized state, but physical stability and surfactant burden must be controlled [57].

Polymeric nanoparticles offer wide compositional flexibility through materials such as PLGA, polycaprolactone, chitosan, and amphiphilic block copolymers. They can provide sustained release and surface functionalization, but residual solvent, polymer molecular weight, degradation behavior, and reproducibility of particle formation become important CQAs. Micelles are particularly useful for solubilizing hydrophobic compounds within a core, while nanocrystals minimize excipient burden by reducing the drug itself to a nanoscale solid stabilized by surfactants or polymers. Each architecture therefore solves a different formulation problem; none is intrinsically superior.

Size and size distribution are especially consequential because they influence physical stability, dissolution, mucosal interaction, cellular uptake, filtration behavior, and biodistribution. Danaei et al. reviewed how particle size and PDI can change the clinical behavior of lipid nanocarriers [58]. A narrow PDI improves interpretability but does not guarantee biological superiority. Similarly, a highly negative or positive zeta potential may improve colloidal stability while altering protein adsorption or mucosal interactions. Formulation optimization should therefore use multivariate design to balance drug loading, size, PDI, surface charge, release, and stability rather than maximizing a single response.

## 5. Quercetin Nanoformulations

Quercetin nanoformulations have expanded from relatively simple lipid dispersions and polymeric nanoparticles to route-specific and hybrid platforms [5,6]. The dominant development objective is to overcome poor water solubility while reducing rapid loss of bioavailable aglycone. Lipid systems are particularly attractive for oral delivery because they can maintain quercetin in a solubilized or molecularly dispersed state during gastrointestinal transit. Hädrich et al. produced a lipid-based quercetin nanocarrier using castor oil, PEG 660 stearate, and lecithin; the optimized system was approximately 20 nm and showed sustained release associated with quercetin-lipid interactions [16]. Jain et al. developed quercetin-loaded lipid carriers with high entrapment and reported improved antitumor and antimetastatic effects in mice compared with a quercetin suspension [17]. These studies demonstrate the capacity of lipid matrices to protect and solubilize quercetin, although differences in disease models and dosing prevent direct comparison of effect size.

SLNs and NLCs add the possibility of sustained release and improved physical protection. Ahmad et al. reported quercetin-loaded SLNs for an ovariectomized rat model, with particles around 173 nm and substantially greater systemic exposure than free quercetin; the formulation also improved osteoprotective endpoints [18]. Such results are mechanistically plausible because a lipid matrix can promote dissolution and prolong release, but translation requires stability studies demonstrating that quercetin is not expelled during lipid crystallization and storage. NLCs can reduce this risk by introducing imperfections into the solid lipid structure. For both SLNs and NLCs, lipid polymorphism, drug localization, and the effect of digestion products on intestinal solubilization should be considered alongside conventional size and EE measurements.

Polymeric systems provide a different control mechanism. PLGA and related polymers can encapsulate quercetin, reduce immediate precipitation, and produce sustained release. Zhou et al. used quercetin-loaded polymeric nanoparticles in a triple-negative breast cancer model and linked improved therapeutic activity to inhibition of urokinase-type plasminogen activator signaling [19]. Chitosan is particularly interesting for oral and mucosal delivery because it is cationic and mucoadhesive, and Lawson's review identified numerous quercetin-chitosan systems investigated in cancer, skin injury, cataract, and oxidative-stress models [14]. Nevertheless, chitosan is not a single uniform excipient: molecular weight, degree of deacetylation, ionic cross-linking, pH, and counterions can all change particle behavior. Standardization is therefore a major translational issue.

Alternative structures broaden the route-specific possibilities. Quercetin nanocochleates reported by Kapare et al. had a mean particle size of about 206 nm and approximately 76% encapsulation efficiency; the formulation increased Cmax and AUC and showed greater cytotoxic activity against MCF-7 cells than unformulated quercetin [20]. Cyclodextrin-containing powders have also been studied for nasal delivery. Manta et al. found that

intranasal administration of quercetin-cyclodextrin systems in rats produced measurable systemic and brain exposure where oral exposure was comparatively limited [23]. These observations support route engineering, but intranasal translation requires local tolerability, deposition, mucociliary clearance, dose-volume feasibility, and repeated-dose safety to be evaluated explicitly.

Human pharmacokinetic studies are particularly valuable because they show that formulation effects observed in animals can translate to altered exposure. Joseph et al. evaluated a natural self-emulsifying reversible hybrid-hydrogel formulation in 16 healthy volunteers and reported markedly higher free and total quercetin exposure than unformulated quercetin, alongside a large increase in apparent solubility [21]. Solnier et al. subsequently evaluated a micellar quercetin formulation in a diet-controlled crossover pilot study; at matched 500 mg dosing, the formulated product produced approximately sevenfold higher 24-h exposure than standard quercetin, while higher doses produced still greater absorption [22]. These findings are encouraging but should not be treated as interchangeable estimates because the formulations, analytical methods, dose normalization, and definition of total versus free quercetin differ.

The food matrix and colonic metabolism remain relevant even when advanced delivery systems are used. Di Pede et al. showed in an in vitro human fecal fermentation model that phytosome formulation altered the microbial degradation kinetics of quercetin, indicating that delivery systems can influence not only small-intestinal absorption but also the substrate reaching colonic microbiota [24]. Earlier human work also demonstrated substantial variability in quercetin pharmacokinetics across oral carriers [12]. Thus, future oral nanocarrier studies should measure both parent and conjugated metabolites, report fed/fasted conditions, and consider whether improved systemic exposure arises from enhanced dissolution, altered intestinal processing, or changes in metabolism.

Therapeutically, quercetin nanoformulations have been investigated most heavily in cancer, inflammation, oxidative injury, dermatology, and metabolic or degenerative disorders [13,25-28]. The main recurring advantages are enhanced solubility, greater cellular uptake, sustained release, and stronger responses in preclinical models. However, the clinical evidence base for disease treatment remains small compared with the formulation literature. Accordingly, the most defensible conclusion is that nanoformulation has established pharmacokinetic and pharmaceutical value for quercetin, whereas disease-specific clinical benefit remains a separate hypothesis requiring adequately powered trials.

## 6. Curcumin Nanoformulations

Curcumin is one of the most extensively nanoformulated natural products. The early rationale was straightforward: a carrier that disperses curcumin in water and protects it from degradation could overcome the inability of native crystalline curcumin to generate sustained systemic exposure [29,31]. Bisht et al. provided an influential proof of concept by encapsulating curcumin in polymeric nanoparticles with a size near 50 nm; nanocurcumin was readily dispersible and retained anticancer activity in pancreatic cancer cell lines [47]. Mohanty and Sahoo later reported an aqueous nanoparticulate formulation around 192 nm that improved stability and produced a longer in vivo half-life and greater bioavailability than native curcumin in mice [48]. These studies established two enduring design goals: physical stabilization of the payload and maintenance of biologically accessible curcumin after administration.

Polymeric nanoparticles remain attractive because degradation rate and release can be tuned through polymer composition and molecular weight. PLGA, chitosan, polycaprolactone, and block-copolymer micelles have been studied extensively [40,44,45]. Polymeric carriers also facilitate co-delivery with cytotoxic drugs, which is relevant to cancer because curcumin is frequently investigated as a chemosensitizer or pathway modulator [44]. The scientific challenge is to separate true combination synergy from changes in exposure produced by the carrier. Rigorous designs should therefore compare free-free, free-encapsulated, encapsulated-free, and co-encapsulated combinations at equivalent drug doses and include release kinetics in biologically relevant media.

Lipid-based curcumin delivery includes liposomes, SLNs, NLCs, nanoemulsions, and lipid-polymer hybrids [40-46]. Liposomes can incorporate curcumin within the bilayer and are amenable to PEGylation or ligand attachment, whereas SLNs and NLCs provide a solid or semi-solid hydrophobic matrix. In a direct comparison for brain delivery, Malvajerd et al. optimized curcumin-loaded SLNs and NLCs and found higher brain exposure with the NLC formulation than with SLNs or free curcumin after intravenous dosing in rats [46]. More recently, Liakopoulou et al. compared curcumin-loaded SLNs, NLCs, and nanoemulsions for skin applications; the systems showed high encapsulation, with NLCs providing favorable longer-term stability and skin penetration [52]. These examples illustrate why carrier selection must be linked to route and therapeutic objective rather than discussed as a universal hierarchy.

Nanoemulsions and micelles are particularly useful when the principal barrier is solubilization. Their performance depends on surfactant composition, dilution stability, digestion, and whether the compound remains solubilized after transition from formulation to biological fluids. For oral products, self-emulsifying systems can generate fine dispersions in the gastrointestinal tract and may reduce dependence on dissolution of the original crystal. However, very high surfactant concentrations can cause GI intolerance or complicate chronic administration. Micelles can produce high apparent solubility but may dissociate

below the critical micelle concentration or exchange payload with plasma proteins after systemic administration. In vitro release therefore needs to be interpreted together with dilution, protein-binding, and in vivo PK data.

Curcumin nanocrystals and nanosuspensions take a different approach by maximizing drug fraction and increasing dissolution rate without a large carrier mass. They may be attractive for oral products where targeting is unnecessary, but nanosuspensions still require stabilizers and are vulnerable to Ostwald ripening, aggregation, or crystal growth. Hybrid systems, nanogels, dendrimers, mesoporous materials, and stimuli-responsive carriers offer greater functional complexity [40,49-54]. Such platforms can be useful experimentally, particularly for tumor targeting, yet each additional component increases the analytical burden and creates new potential failure modes in scale-up and storage.

Human bioavailability research provides an important benchmark for whether nanoscale engineering is necessary. Piperine increased curcumin exposure in the classic Shoba study by inhibiting metabolic conjugation [35], demonstrating that metabolism can be as important as dissolution. Shaikh et al. reported that nanoparticle encapsulation improved oral bioavailability in animals beyond a curcumin-piperine comparator [36]. Sasaki et al. developed a colloidal submicron dispersion (Theracurmin) that produced substantially higher AUC than curcumin powder in healthy volunteers [37]. Later reviews of clinical formulations have documented enhanced-bioavailability products using colloidal dispersions, micelles, phospholipids, polysaccharides, and related approaches [32,39]. These results confirm that formulation can change exposure, but they do not establish that the platform with the largest AUC increase will necessarily have the best efficacy, safety, cost, or manufacturability.

The curcumin field also illustrates the need for chemical rigor. Nelson et al. emphasized that curcumin can undergo degradation and interfere with several assay formats [33]. Nanoencapsulation may reduce degradation, but it does not remove the need to measure actual curcumin concentration and degradation products during biological testing. A robust formulation paper should therefore characterize curcumin content after manufacturing and storage, verify release of chemically intact drug, use appropriate blank-carrier controls, and interpret fluorescence-based assays cautiously. This level of analytical discipline is essential if the very large preclinical literature is to generate reproducible translational hypotheses.

**Table 2. Representative nanoformulation strategies for quercetin and curcumin.**

| Bioactive or system | Representative composition or strategy | Typical preparation principle | Reported formulation or PK finding | Key limitation |
|---|---|---|---|---|
| Quercetin / lipid nanocarrier | Castor oil + PEG 660 stearate + lecithin | Hot solvent diffusion / phase inversion | ~20 nm carrier; sustained release reported [16] | Dilution/digestion behavior and long-term lipid stability need control. |
| Quercetin / SLN | Solid lipid matrix + surfactant | Hot homogenization/emulsification | ~173 nm; higher exposure and osteoprotective activity in rats [18] | Lipid crystallization may expel drug during storage. |
| Quercetin / polymeric NP | PLGA or related biodegradable polymer | Nanoprecipitation/emulsion-solvent methods | Improved tumor-model activity and sustained delivery reported [19] | Residual solvent, polymer variability, and scale-up. |
| Quercetin / nanocochleate | Phospholipid-based cochleate structure | Trapping/precipitation approach | 205.6 nm, 76.36% EE; increased Cmax/AUC vs pure quercetin [20] | Limited clinical experience and complex structural characterization. |
| Quercetin / self-emulsifying hybrid hydrogel | Fenugreek galactomannan-based hybrid | Self-emulsifying encapsulation | Human study reported 18.6-fold free and 62-fold total quercetin exposure vs unformulated comparator [21] | Single study; analyte definition and comparator affect fold-change. |
| Curcumin / polymeric nanocurcumin | Cross-linked amphiphilic copolymer | Micellar polymerization/encapsulation | ~50 nm, aqueous dispersibility and retained anticancer activity | Early proof-of-concept; needs scalable manufacturing and |

| | | | | |
|---|---|---|---|---|
| | | | [47] | in vivo confirmation. |
| Curcumin / aqueous nanoparticle | Glyceryl monooleate + stabilizer system | Nanoparticle dispersion | ~192 nm; improved stability and longer in vivo exposure in mice [48] | Preclinical; formulation-specific safety and reproducibility. |
| Curcumin / SLN and NLC | Solid lipid vs mixed solid/liquid lipid matrices | Design-of-experiments optimized lipid NP process | NLC produced higher brain exposure than SLN/free curcumin after IV rat dosing [46] | Parenteral lipid quality, biodistribution, and chronic safety. |
| Curcumin / colloidal submicron dispersion | Highly dispersed curcumin formulation (Theracurmin) | Colloidal dispersion technology | Human AUC substantially greater than curcumin powder [37] | PK enhancement does not itself demonstrate clinical efficacy. |
| Curcumin / lipid skin nanocarriers | SLN, NLC and nanoemulsion | Lipid dispersion methods | High encapsulation; NLC favored long-term stability/skin penetration [52] | Topical results cannot be extrapolated to oral/systemic delivery. |

*EE, encapsulation efficiency; IV, intravenous. Numerical values are study-specific and should not be compared across studies without dose and analytical normalization.*

**7. Comparative Pharmacokinetics and Therapeutic Evidence**

For both quercetin and curcumin, the strongest evidence that formulation matters is pharmacokinetic rather than therapeutic. Quercetin human studies demonstrate that absorption depends on chemical form, food matrix, and formulation, with substantial increases in exposure reported for hybrid-hydrogel and micellar products [11,21,22]. Curcumin studies similarly show large formulation-dependent differences in systemic exposure [32,35,37,39]. However, the apparent magnitude of enhancement is sensitive to the comparator. A formulation compared with crystalline aglycone may show a much larger fold increase than one compared with an already dispersed or food-associated preparation. Fold-change should therefore always be accompanied by absolute dose-normalized AUC, Cmax, Tmax, analyte definition, and sampling duration.

A second issue is whether the parent molecule is the correct pharmacokinetic marker. Quercetin circulates largely as glucuronidated, sulfated, and methylated metabolites [7,9,11]. Curcumin is also extensively conjugated and reduced [29-32,53]. Some bioactivity may arise from metabolites, local intestinal effects, or tissue deconjugation rather than from high concentrations of unchanged parent compound. Consequently, a formulation that raises total plasma analytes may not have the same biological implications as one that raises free aglycone. Future comparative PK studies should quantify parent and major metabolites separately when technically feasible and should report whether enzymatic hydrolysis was used before analysis.

Therapeutic studies span cancer, inflammatory disease, neurodegeneration, metabolic disorders, cardiovascular conditions, dermatologic disease, wound healing, and oxidative injury [25,26,41-54]. In cancer models, nanocarriers may increase local exposure, exploit enhanced permeability in selected animal tumors, or support active ligand targeting. Yet the enhanced permeability and retention effect is variable in human tumors, and tumor accumulation alone does not establish therapeutic advantage. Similar caution applies to brain targeting: increased brain AUC in rodents, as shown for curcumin NLCs [46] or intranasal quercetin systems [23], is a valuable delivery result but requires confirmation of regional distribution, pharmacodynamic engagement, and chronic safety.

The therapeutic literature is dominated by oncology, in part because both compounds modulate multiple stress, inflammatory, apoptotic, and proliferation-associated pathways and because nanoparticles provide an intuitive route to tumor-directed delivery. Quercetin systems have been evaluated in breast, melanoma, liver, and colorectal models, with reports of improved tumor inhibition or cellular effects after encapsulation [17,19,25,26]. Curcumin nanoformulations have been tested across a still wider range of malignancies, including pancreatic, breast, colorectal, and brain tumor models [42-49,54]. These findings support further investigation but are vulnerable to familiar preclinical biases: high local doses, short treatment duration, tumor models with unusually permeable vasculature, and endpoints based mainly on tumor volume or cell viability. Translation would be strengthened by pharmacokinetic-pharmacodynamic

modeling, comparison against clinically relevant standard treatments, and demonstration that the nanoformulation improves efficacy at equal or lower systemic exposure rather than only enabling administration of a poorly soluble compound.

Inflammatory, neurological, metabolic, and dermatological indications may offer different opportunities. For chronic inflammatory diseases, the oral route is attractive, but repeated-dose tolerability and excipient exposure become more important than maximal peak concentration. Laurindo et al. summarized curcumin nanomedicines across inflammatory and immune-mediated disorders, whereas quercetin reviews describe anti-inflammatory applications that remain largely preclinical [8,41]. For neurological indications, brain exposure is a prerequisite but not a sufficient endpoint. The higher brain AUC observed with curcumin NLCs in rats [46] and the brain delivery achieved by intranasal quercetin-cyclodextrin systems [23] should be followed by studies of regional drug distribution, target engagement, neurobehavioral outcomes, and nasal or systemic safety during prolonged administration. For skin delivery, local retention may be preferable to high plasma exposure, as illustrated by quercetin topical systems [13] and curcumin lipid nanocarriers [52].

An underappreciated comparative issue is route-specific dose capacity. Plant polyphenols are often studied at hundreds of milligrams orally, but highly engineered parenteral or intranasal nanosystems may not practically carry equivalent doses. A formulation that performs well in a cell assay at microgram quantities may therefore be unsuitable for a human product if drug loading is low or excipient burden becomes excessive. Dose capacity should be incorporated early into the target product profile together with desired exposure, dosing frequency, route, container closure, and storage conditions. This favors high-loading platforms such as nanocrystals for some oral applications, while lower-loading targeted carriers may be justified only when tissue selectivity substantially reduces the required dose.

The most persuasive future studies will therefore connect a defined formulation attribute to a mechanistic PK change and then to a clinically relevant pharmacodynamic endpoint. Examples include demonstrating that a stable sub-200-nm oral carrier prevents precipitation, increases intestinal solubilized fraction, raises dose-normalized AUC, and improves a validated biomarker at an exposure that is tolerable in repeated dosing. Without this chain of evidence, improved in vitro cytotoxicity or antioxidant activity can remain disconnected from translational benefit.

## 8. Formulation Development and Characterization

A nanocarrier should be characterized as a pharmaceutical product, not merely as a particle. Core CQAs include mean particle or droplet size, full size distribution and PDI, zeta potential where relevant, drug content, EE or loading, morphology, solid-state form, chemical purity, in vitro release, dilution stability, and storage stability. For lipid systems, lipid crystallinity and polymorphic transitions can alter loading and release. For polymeric systems, molecular weight, residual monomer or solvent, degradation rate, and polymer-drug interactions are important. For nanoemulsions and self-emulsifying systems, robustness to dilution, dispersion time, droplet size after digestion, and precipitation tendency should be evaluated [55-58].

Method selection should be orthogonal. DLS is efficient for hydrodynamic size but can be biased by small populations of large particles; TEM or cryo-TEM provides morphological confirmation but examines a limited sample. Differential scanning calorimetry and X-ray diffraction can establish whether quercetin or curcumin remains crystalline or becomes molecularly dispersed/amorphous. FTIR, Raman, and nuclear magnetic resonance can support interaction studies, while validated HPLC or LC-MS methods are required for content, degradation, release, and PK measurements. Analytical specificity is particularly important for curcumin because degradation products and fluorescence can confound some assays [33].

QbD is well suited to nanoformulation because critical material attributes and process parameters interact strongly. A rational development sequence defines the quality target product profile, identifies CQAs, performs risk assessment, uses designed experiments to map the design space, and establishes a control strategy [64,65,67]. Parameters such as lipid-to-drug ratio, polymer concentration, surfactant concentration, solvent-to-aqueous phase ratio, homogenization pressure, sonication energy, mixing rate, and temperature should be related quantitatively to size, PDI, loading, release, and stability. This approach produces more transferable knowledge than optimizing one variable at a time.

## 9. Safety, Regulatory Translation, and Pharmaceutical Quality

Nanocarrier safety cannot be inferred from the safety reputation of the plant compound. Excipients that are acceptable in conventional dosage forms may behave differently at high interfacial area or after parenteral administration, and surface charge, impurities, degradation products, and repeated exposure can alter toxicity. Blank-carrier controls are therefore essential in cell and animal studies. Chronic oral systems also require attention to surfactant load, lipid digestion, mucosal effects, and interactions with concomitant medicines. For curcumin, coadministration with piperine illustrates a broader point: pharmacokinetic enhancement through metabolic inhibition can increase the exposure of other xenobiotics as well as the intended compound [35].

Regulatory evaluation of nanomaterial-containing drug products is product-specific. FDA guidance emphasizes

comprehensive characterization of nanomaterial attributes, manufacturing controls, stability, and the relationship between nanoscale properties and product performance [60]. Regulatory analyses of approved and investigational nanomedicines similarly show that nanomaterial identity, size, surface properties, and manufacturing process can be integral to safety and efficacy [4,59,66]. The challenge for quercetin and curcumin is that many published formulations are academic prototypes with no demonstrated scale-up path. A clinically credible formulation should use excipients with an acceptable route-specific safety basis, specify raw-material grades, define in-process controls, and demonstrate batch comparability after scale-up.

Particulate and foreign-matter control is an additional quality issue for oral nanoformulations. Pandey and Chavda's 2026 review of particulate matter in oral dosage forms identifies raw materials, manufacturing equipment, facilities and utilities, packaging components, cleaning residues, personnel, and process design as interconnected contamination sources [62]. This perspective is directly relevant to quercetin and curcumin nanoproducts because nanosuspensions, lipid dispersions, spray-dried intermediates, and capsule or tablet conversions introduce multiple opportunities for both intrinsic particles and extrinsic foreign matter. A risk-based program should distinguish the intended nanostructure from unintended visible or subvisible contamination, establish product-specific particulate baselines, and investigate excursions using complementary analytical techniques. Their proposed toolbox includes microscopy for morphology, FTIR and Raman spectroscopy for organic identification, SEM-EDS for morphology and elemental composition, and X-ray fluorescence or related elemental methods when inorganic contamination is suspected. The broader implication is that a nanoscale active-delivery system does not eliminate conventional GMP particulate risks; instead, developers must control both engineered particle attributes and unintended contaminants. Pajander et al. likewise showed that combining light microscopy, SEM/EDX, FTIR, and surface-sensitive methods can improve source attribution for foreign matter in solid dosage forms [61].

Stability specifications should address aggregation, Ostwald ripening, payload leakage, crystal growth, lipid oxidation, polymer hydrolysis, pH drift, and chemical degradation of the bioactive. For oral liquid nanodispersions, microbial preservation and container-closure compatibility also matter. Conversion to a dry intermediate by lyophilization or spray drying may improve shelf life but can change redispersibility and size distribution. Therefore, redispersed product - not only the freshly prepared dispersion - should meet the clinically relevant CQA specification.

Finally, bioavailability enhancement must not be used as a surrogate for benefit-risk. A formulation that produces very high exposure could increase off-target effects, alter drug interactions, or deliver metabolites to tissues at concentrations not achieved through diet. Human dose-escalation and repeated-dose studies should therefore be designed around exposure margins, safety pharmacology, and relevant biomarkers. This is especially important for products positioned between pharmaceutical, nutraceutical, and functional-food categories, where regulatory requirements and allowable claims differ substantially.

## 10. Clinical Translation, Research Gaps, and Future Directions

The field has moved beyond proof that quercetin and curcumin can be put into nanoparticles. The translational problem is now selection: which formulations provide enough added value to justify their complexity? For oral delivery, simple lipid dispersions, micelles, self-emulsifying systems, or nanocrystals may be preferable when the main objective is solubility and exposure. For local skin or mucosal delivery, retention and penetration can justify NLCs, nanogels, or vesicular systems. For parenteral cancer applications, more complex targeted carriers may be rational, but they require stringent sterility, endotoxin, biodistribution, immunological, and manufacturing controls. Platform complexity should therefore increase only when it addresses a defined biological barrier.

Several research gaps are common to both compounds. First, head-to-head comparisons among nanocarrier classes are rare. Studies typically compare one optimized nanoformulation with free compound, making it impossible to determine whether a simpler platform would perform equally well. Second, many reports emphasize particle size and EE but provide limited information on chemical stability, batch-to-batch variability, or scale-up. Third, pharmacokinetic sampling often does not distinguish parent from conjugated metabolites. Fourth, therapeutic studies frequently use doses or administration routes that are difficult to translate. Fifth, long-term nanocarrier toxicity and excipient exposure receive less attention than acute efficacy.

Future development should combine mechanistic formulation science with clinically relevant endpoints. Comparative studies should use standardized reference formulations, dose normalization, validated bioanalytical methods, and prespecified PK metrics. Physiologically based pharmacokinetic modeling could help integrate dissolution, metabolism, and tissue distribution, particularly when multiple metabolites contribute to activity. Advanced in vitro intestinal models and biorelevant digestion systems can improve understanding of oral lipid formulations before animal testing. For targeted systems, quantitative ligand density, protein-corona effects, receptor expression, and actual tissue exposure should be measured rather than inferred from uptake images.

A final priority is reproducibility. Formulations intended

for translation should be described with sufficient detail to reproduce lipid grade, polymer molecular weight, excipient ratios, processing energy, temperature history, filtration, and drying conditions. Scale-up studies should demonstrate that the same CQAs are maintained when moving from probe sonication or small-batch solvent evaporation to industrially feasible homogenization, mixing, or continuous processes. Regulatory engagement at an early stage can then focus development on the attributes most likely to affect clinical performance [59,60].

**Table 3. Translational decision framework for quercetin and curcumin nanoproducts.**

| Development domain | Critical questions / CQAs | Common failure mode | Recommended evidence before translation |
|---|---|---|---|
| Drug substance | Which chemical form is loaded? Is the parent stable during processing/storage? | Unrecognized degradation, polymorphic change, or variable raw material | Validated identity/purity assay, degradation profile, solid-state characterization, supplier controls. |
| Particle attributes | Are size, PDI, morphology, charge, loading, and release linked to performance? | Optimizing size alone while other CQAs drift | Orthogonal sizing/microscopy; loading and release assays; mechanistic relation to PK. |
| Oral performance | Does the payload remain solubilized after dilution/digestion? | Precipitation after administration; surfactant-dependent artifacts | Biorelevant dissolution/digestion, permeability models, fed/fasted PK, parent + metabolite analysis. |
| Safety | Does the carrier alter toxicity, immunity, GI tolerance, or interactions? | Attributing carrier effects to quercetin/curcumin | Blank-carrier controls, repeated-dose tolerability, route-specific excipient justification. |
| Manufacturing | Can scale-up preserve CQAs and chemical integrity? | Batch drift with changes in mixing, homogenization, solvent removal, or drying | QbD design space, in-process controls, scale-up comparability, GMP-compatible process. |
| Stability | Does size or payload state change over shelf life? | Aggregation, crystal growth, leakage, oxidation, degradation | ICH-oriented stability plan with redispersibility and performance testing after storage. |
| Contamination control | How are engineered nanoparticles distinguished from unintended particulate matter? | Foreign particles from equipment, raw materials, packaging, or cleaning | Risk-based particulate baseline; microscopy plus FTIR/Raman/SEM-EDS as needed [61,62]. |
| Clinical relevance | Is higher exposure connected to a validated endpoint? | Equating AUC increase with therapeutic efficacy | Dose-normalized PK, pharmacodynamic biomarker, adequate comparator, safety and efficacy trial. |

## 11. Conclusions

Nanotechnology-based delivery has a strong pharmaceutical rationale for both quercetin and curcumin, but the two compounds should not be treated as chemically interchangeable. Quercetin is a flavonol whose oral disposition depends on glycoside form, dissolution, and extensive conjugation, whereas curcumin is a diarylheptanoid curcuminoid with particularly poor aqueous solubility, instability, rapid metabolism, and analytical complexities. Lipid nanoparticles, liposomes,

nanoemulsions, polymeric nanoparticles, micelles, chitosan systems, nanocrystals, and hybrid platforms can improve solubilization, stability, release control, and systemic or tissue exposure. Human studies confirm that formulation can substantially increase exposure for selected quercetin and curcumin products, while preclinical studies provide extensive evidence of improved pharmacodynamic responses.

The major limitation is translation from formulation performance to proven therapeutic benefit. Cross-study bioavailability claims are not directly comparable, and increased AUC should not be interpreted as clinical efficacy without appropriate pharmacodynamic and safety evidence. Future work should prioritize head-to-head platform comparisons, validated measurement of parent compounds and metabolites, route-specific safety, QbD-driven scale-up, long-term stability, and regulatory-quality characterization. For oral products, engineered nanoparticle control must also be integrated with conventional particulate and contamination management. These steps would shift the field from increasingly elaborate proof-of-concept nanostructures toward reproducible products whose added complexity is justified by measurable clinical value.

**References**


1. Patra JK, Das G, Fraceto LF, Campos EVR, Rodriguez-Torres MP, Acosta-Torres LS, et al. Nano based drug delivery systems: recent developments and future prospects. J Nanobiotechnology. 2018;16:71. doi:10.1186/s12951-018-0392-8.
2. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. Nat Rev Drug Discov. 2021;20(2):101-124. doi:10.1038/s41573-020-0090-8.
3. Anselmo AC, Mitragotri S. Nanoparticles in the clinic: an update. Bioeng Transl Med. 2019;4(3):e10143. doi:10.1002/btm2.10143.
4. D'Mello SR, Cruz CN, Chen ML, Kapoor M, Lee SL, Tyner KM. The evolving landscape of drug products containing nanomaterials in the United States. Nat Nanotechnol. 2017;12(6):523-529. doi:10.1038/nnano.2017.67.
5. Tomou EM, Papakyriakopoulou P, Saitani EM, Valsami G, Pippa N, Skaltsa H. Recent advances in nanoformulations for quercetin delivery. Pharmaceutics. 2023;15(6):1656. doi:10.3390/pharmaceutics15061656.
6. Kaur S, Goyal A, Rai A, Sharma A, Ugoeze KC, Singh I. Quercetin nanoformulations: recent advancements and therapeutic applications. Adv Nat Sci Nanosci Nanotechnol. 2023;14(3):033002. doi:10.1088/2043-6262/acedaa.
7. Wang W, Sun C, Mao L, Ma P, Liu F, Yang J, et al. The biological activities, chemical stability, metabolism and delivery systems of quercetin: a review. Trends Food Sci Technol. 2016;56:21-38. doi:10.1016/j.tifs.2016.07.004.
8. Li Y, Yao J, Han C, Yang J, Chaudhry MT, Wang S, et al. Quercetin, inflammation and immunity. Nutrients. 2016;8(3):167. doi:10.3390/nu8030167.
9. Dabeek WM, Marra MV. Dietary quercetin and kaempferol: bioavailability and potential cardiovascular-related bioactivity in humans. Nutrients. 2019;11(10):2288. doi:10.3390/nu11102288.
10. Boots AW, Haenen GRMM, Bast A. Health effects of quercetin: from antioxidant to nutraceutical. Eur J Pharmacol. 2008;585(2-3):325-337. doi:10.1016/j.ejphar.2008.03.008.
11. Graefe EU, Wittig J, Mueller S, Riethling AK, Uehleke B, Drewelow B, et al. Pharmacokinetics and bioavailability of quercetin glycosides in humans. J Clin Pharmacol. 2001;41(5):492-499. doi:10.1177/00912700122010366.
12. Kaushik D, O'Fallon K, Clarkson PM, Dunne CP, Conca KR, Michniak-Kohn B. Comparison of quercetin pharmacokinetics following oral supplementation in humans. J Food Sci. 2012;77(11):H231-H238. doi:10.1111/j.1750-3841.2012.02934.x.
13. Wadhwa K, Kadian V, Puri V, Bhardwaj BY, Sharma A, Pahwa R, et al. New insights into quercetin nanoformulations for topical delivery. Phytomedicine Plus. 2022;2(2):100257. doi:10.1016/j.phyplu.2022.100257.
14. Lawson MK. Improvement of therapeutic value of quercetin with chitosan nanoparticle delivery systems and potential applications. Int J Mol Sci. 2023;24(4):3293. doi:10.3390/ijms24043293.
15. Zhao XY, Deng Y, Xue X, Liao L, Zhou M, Peng C, et al. Research progress of quercetin delivery systems. Curr Pharm Des. 2022;28. doi:10.2174/1381612828666220317141923.
16. Hadrich G, Monteiro SO, Rodrigues MR, de Lima VR, Putaux JL, Bidone J, et al. Lipid-based nanocarrier for quercetin delivery: system characterization and molecular interactions studies. Drug Dev Ind Pharm. 2016;42(7):1165-1173. doi:10.3109/03639045.2015.1118491.
17. Jain AS, Shah SM, Nagarsenker MS, Nikam Y, Gude RP, Steiniger F, et al. Lipid colloidal carriers for improvement of anticancer activity of orally delivered quercetin: formulation, characterization and establishing in vitro-in vivo advantage. J Biomed Nanotechnol. 2013;9(7):1230-1240. doi:10.1166/jbn.2013.1636.
18. Ahmad N, Banala VT, Kushwaha P, Karvande A, Sharma S, Tripathi AK, et al. Quercetin-loaded solid lipid nanoparticles improve osteoprotective activity in an ovariectomized rat model: a preventive strategy for

post-menopausal osteoporosis. RSC Adv. 2016;6. doi:10.1039/C6RA17141A.
19. Zhou Y, Chen D, Xue G, Yu S, Yuan C, Huang M, et al. Improved therapeutic efficacy of quercetin-loaded polymeric nanoparticles on triple-negative breast cancer by inhibiting uPA. RSC Adv. 2020;10. doi:10.1039/D0RA04231E.
20. Kapare HS, Patil ND, Bhosale M, Kulkarni D, Bhole RP. Nanocochleate-based delivery of quercetin with enhanced therapeutic potential: formulation, cytotoxicity and pharmacokinetics study. Future J Pharm Sci. 2024;10. doi:10.1186/s43094-024-00732-z.
21. Joseph A, Shanmughan P, Balakrishnan AM, Maliakel B. Enhanced bioavailability and pharmacokinetics of a natural self-emulsifying reversible hybrid-hydrogel system of quercetin: a randomized double-blinded comparative crossover study. ACS Omega. 2022;7. doi:10.1021/acsomega.2c05929.
22. Solnier J, Zhang Y, Roh K, Kuo YC, Du M, Wood S, et al. A pharmacokinetic study of different quercetin formulations in healthy participants: a diet-controlled, crossover, single- and multiple-dose pilot study. Evid Based Complement Alternat Med. 2023;2023:9727539. doi:10.1155/2023/9727539.
23. Manta K, Papakyriakopoulou P, Nikolidaki A, Balafas E, Kostomitsopoulos N, Banella S, et al. Comparative serum and brain pharmacokinetics of quercetin after oral and nasal administration to rats as lyophilized complexes with beta-cyclodextrin derivatives and their blends with mannitol/lecithin microparticles. Pharmaceutics. 2023;15(8):2036. doi:10.3390/pharmaceutics15082036.
24. Di Pede G, Bresciani L, Calani L, Petrangolini G, Riva A, Allegrini P, et al. The human microbial metabolism of quercetin in different formulations: an in vitro evaluation. Foods. 2020;9(8):1121. doi:10.3390/foods9081121.
25. Zang X, Cheng M, Zhang X, Chen X. Quercetin nanoformulations: a promising strategy for tumor therapy. Food Funct. 2021;12. doi:10.1039/D1FO00851J.
26. Eity TA, Bhuia MS, Chowdhury R, Ahmmed S, Sheikh S, Akter R, et al. Therapeutic efficacy of quercetin and its nanoformulation both the mono- or combination therapies in the management of cancer: an update with molecular mechanisms. J Trop Med. 2024;2024:5594462. doi:10.1155/2024/5594462.
27. da Silva TA, Gomes JH, de Bulhoes LCG, dos Santos Neto RM, Basilio Junior ID, de Moura MABF, et al. Therapeutic potential of quercetin based on nanotechnology: a review. Rev Virtual Quim. 2019;11. doi:10.21577/1984-6835.20190096.
28. Kapare HS, Kanadje S, Bhole RP. Quercetin nano-formulations as a potential approach for skin cancer. Pharm Nanotechnol. 2024. doi:10.2174/0122117385332427241112034005.
29. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. Mol Pharm. 2007;4(6):807-818. doi:10.1021/mp700113r.
30. Hewlings SJ, Kalman DS. Curcumin: a review of its effects on human health. Foods. 2017;6(10):92. doi:10.3390/foods6100092.
31. Prasad S, Tyagi AK, Aggarwal BB. Recent developments in delivery, bioavailability, absorption and metabolism of curcumin: the golden pigment from golden spice. Cancer Res Treat. 2014;46(1):2-18. doi:10.4143/crt.2014.46.1.2.
32. Stohs SJ, Chen O, Ray SD, Ji J, Bucci LR, Preuss HG. Highly bioavailable forms of curcumin and promising avenues for curcumin-based research and application: a review. Molecules. 2020;25(6):1397. doi:10.3390/molecules25061397.
33. Nelson KM, Dahlin JL, Bisson J, Graham J, Pauli GF, Walters MA. The essential medicinal chemistry of curcumin. J Med Chem. 2017;60(5):1620-1637. doi:10.1021/acs.jmedchem.6b00975.
34. Padmanaban G, Nagaraj VA. Curcumin may defy medicinal chemists. ACS Med Chem Lett. 2017;8(3):274. doi:10.1021/acsmedchemlett.7b00051.
35. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PSSR. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med. 1998;64(4):353-356. doi:10.1055/s-2006-957450.
36. Shaikh J, Ankola DD, Beniwal V, Singh D, Kumar MNVR. Nanoparticle encapsulation improves oral bioavailability of curcumin by at least 9-fold when compared to curcumin administered with piperine as absorption enhancer. Eur J Pharm Sci. 2009;37(3-4):223-230. doi:10.1016/j.ejps.2009.02.019.
37. Sasaki H, Sunagawa Y, Takahashi K, Imaizumi A, Fukuda H, Hashimoto T, et al. Innovative preparation of curcumin for improved oral bioavailability. Biol Pharm Bull. 2011;34(5):660-665. doi:10.1248/bpb.34.660.
38. Liu W, Zhai Y, Heng X, Che FY, Chen W, Sun D, et al. Oral bioavailability of curcumin: problems and advancements. J Drug Target. 2016;24(8):694-702. doi:10.3109/1061186X.2016.1157883.
39. Hegde MG, Girisa S, BharathwajChetty B, Vishwa R, Kunnumakkara AB. Curcumin formulations for better bioavailability: what we learned from clinical trials thus far? ACS Omega. 2023;8. doi:10.1021/acsomega.2c07326.
40. Jacob S, Kather FS, Morsy MA, Boddu SHS, Attimarad M, Shah J, et al. Advances in nanocarrier systems for overcoming formulation challenges of curcumin: current insights. Nanomaterials. 2024;14(8):672. doi:10.3390/nano14080672.
41. Laurindo LF, de Carvalho GM, Zanuso BO, Figueira

ME, Direito R, Goulart RA, et al. Curcumin-based nanomedicines in the treatment of inflammatory and immunomodulated diseases: an evidence-based comprehensive review. Pharmaceutics. 2023;15(1):229. doi:10.3390/pharmaceutics15010229.
42. dos Santos CA, Silva VRP, Ombredane AS, Pinheiro WO, Andrade LR, Pacheco TJA, et al. Pharmacokinetics of curcumin delivered by nanoparticles and the relationship with antitumor efficacy: a systematic review. Pharmaceuticals. 2023;16(7):943. doi:10.3390/ph16070943.
43. Maleki Dizaj S, Alipour M, Dalir Abdolahinia E, Ahmadian E, Eftekhari A, Forouhandeh H, et al. Curcumin nanoformulations: beneficial nanomedicine against cancer. Phytother Res. 2022;36. doi:10.1002/ptr.7389.
44. Alven S, Aderibigbe BA. Efficacy of polymer-based nanocarriers for co-delivery of curcumin and selected anticancer drugs. Nanomaterials. 2020;10(8):1556. doi:10.3390/nano10081556.
45. Araya-Sibaja AM, Wilhelm K, Gonzalez-Aguilar GA, Vega-Baudrit J, Salazar-Lopez NJ, Dominguez-Avila JA, et al. Curcumin loaded and co-loaded nanosystems: a review from a biological activity enhancement perspective. Curr Pharm Biotechnol. 2021. doi:10.2174/2211738508666201228150659.
46. Malvajerd SS, Azadi A, Izadi Z, Kurd M, Dara T, Dibaei M, et al. Brain delivery of curcumin using solid lipid nanoparticles and nanostructured lipid carriers: preparation, optimization, and pharmacokinetic evaluation. ACS Chem Neurosci. 2019;10. doi:10.1021/acschemneuro.8b00510.
47. Bisht S, Feldmann G, Soni S, Ravi R, Karikar C, Maitra A, et al. Polymeric nanoparticle-encapsulated curcumin (nanocurcumin): a novel strategy for human cancer therapy. J Nanobiotechnology. 2007;5:3. doi:10.1186/1477-3155-5-3.
48. Mohanty C, Sahoo SK. The in vitro stability and in vivo pharmacokinetics of curcumin prepared as an aqueous nanoparticulate formulation. Biomaterials. 2010;31(25):6597-6611. doi:10.1016/j.biomaterials.2010.04.062.
49. Wahnou H, El Kebbaj R, Liagre B, Sol V, Limami Y, Duval RE. Curcumin-based nanoparticles: advancements and challenges in tumor therapy. Pharmaceutics. 2025;17(1):114. doi:10.3390/pharmaceutics17010114.
50. Tahvilian M, Tahvilian A, Karimi M, Mahmoudi F, Izadi Z, Malvajerd SS. Recent advances in curcumin drug delivery systems based on nano compounds and their therapeutic application. Adv Ther. 2025. doi:10.1002/adtp.202500414.
51. Rathod NV, Mishra S. Nano-curcumin for cancer therapy: a strategic approach to improve bioavailability and modulate tumor resistance. Chem Biodivers. 2025. doi:10.1002/cbdv.202502012.
52. Liakopoulou A, Letsiou S, Avgoustakis K, Patrinos GP, Lamari FN, Hatziantoniou S. Curcumin-loaded lipid nanocarriers: a targeted approach for combating oxidative stress in skin applications. Pharmaceutics. 2025;17(2):144. doi:10.3390/pharmaceutics17020144.
53. Jude S, Amalraj A, Kunnumakkara AB, Divya C, Loffler BM, Gopi S. Development of validated methods and quantification of curcuminoids and curcumin metabolites and their pharmacokinetic study of oral administration of complete natural turmeric formulation (Cureit) in human plasma via UPLC/ESI-Q-TOF-MS spectrometry. Molecules. 2018;23(10):2415. doi:10.3390/molecules23102415.
54. Hegde MG, Kumar A, Girisa S, Aswani BS, Vishwa R, Sethi G, et al. Nanoformulations of curcumin: an alliance for effective cancer therapeutics. Food Biosci. 2023;55:103095. doi:10.1016/j.fbio.2023.103095.
55. Ghasemiyeh P, Mohammadi-Samani S. Solid lipid nanoparticles and nanostructured lipid carriers as novel drug delivery systems: applications, advantages and disadvantages. Res Pharm Sci. 2018;13(4):288-303. doi:10.4103/1735-5362.235156.
56. Nsairat H, Khater D, Sayed U, Odeh F, Al Bawab A, Alshaer W. Liposomes: structure, composition, types, and clinical applications. Heliyon. 2022;8(5):e09394. doi:10.1016/j.heliyon.2022.e09394.
57. McClements DJ. Nanoemulsions versus microemulsions: terminology, differences, and similarities. Soft Matter. 2012;8(6):1719-1729. doi:10.1039/C2SM06903B.
58. Danaei M, Dehghankhold M, Ataei S, Hasanzadeh Davarani F, Javanmard R, Dokhani A, et al. Impact of particle size and polydispersity index on the clinical applications of lipidic nanocarrier systems. Pharmaceutics. 2018;10(2):57. doi:10.3390/pharmaceutics10020057.
59. Dri DA, Rinaldi F, Carafa M, Marianecci C. Nanomedicines and nanocarriers in clinical trials: surfing through regulatory requirements and physico-chemical critical quality attributes. Drug Deliv Transl Res. 2023;13. doi:10.1007/s13346-022-01262-y.
60. U.S. Food and Drug Administration. Drug Products, Including Biological Products, that Contain Nanomaterials: Guidance for Industry. Silver Spring, MD: FDA; 2022.
61. Stucchi F, Castellano G, Cellesi F. Regulatory framework for polymer-based nanotherapeutics in clinical translation. Front Bioeng Biotechnol. 2026. doi:10.3389/fbioe.2026.1735885.
62. Pandey G, Chavda H. Beyond the status quo: particulate matter standards in oral dosage forms. J Xenobiotics. 2026;16:151. doi:10.3390/jox16040151.
63. Pajander J, Haugshoj KB, Bjorneboe K, Wahlberg P, Rantanen J. Foreign matter identification from solid dosage forms. J Pharm Biomed Anal. 2013;80:116-125. doi:10.1016/j.jpba.2013.02.036.

64. International Council for Harmonisation. ICH Q8(R2): Pharmaceutical Development. Geneva: ICH; 2009.
65. International Council for Harmonisation. ICH Q9(R1): Quality Risk Management. Geneva: ICH; 2023.
66. Anselmo AC, Mitragotri S. Nanoparticles in the clinic: an update post COVID-19 vaccines. Bioeng Transl Med. 2021;6(3):e10246. doi:10.1002/btm2.10246.
67. Bastogne T. Quality-by-design of nanopharmaceuticals - a state of the art. Nanomedicine. 2017;13(7):2151-2157. doi:10.1016/j.nano.2017.05.014.