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Connecting Phytoscience and Nanoengineering: Vesicular, Polymeric, and Green-Synthesized Nanocarriers Revolutionizing Next-Generation Herbal Drug Technologies

Ashutosh Rana[1] **and Ravikant Gupta**[1*]

[1]*School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India*

[*]ravikant491990@gmail.com (Corresponding Author)

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ABSTRACT

Background: The combination of nanotechnology with herbal medicine opens up exciting perspectives for dealing with the disadvantages of phytoconstituents. Being of high medicinal importance, phytoconstituents are characterized by poor water solubility, metabolic instability, low membrane permeability, and gastrointestinal breakdown.

Purpose: To summarize and discuss recent advancements in nanoengineered delivery systems for herbal medicines, paying special attention to their capabilities to improve solubility, stability, bioavailability, targeting, and therapeutic efficacy of phytoconstituents as well as the problems of standardization and safety of herbal nanomedicines.

Methods: A narrative review was performed using peer-reviewed articles, book chapters, and guidelines available within the period from 2000 till 2026, focusing on recent achievements in this area. Relevant literature was identified through PubMed, ScienceDirect, Scopus, Web of Science, and Google Scholar databases as well as guidelines of the World Health Organization (WHO), the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Ministry of AYUSH. Vesicular, lipidic, polymeric, metallic, emulsion-based, and green-synthesized nanoparticles, standardization and nanotoxicology, and computational approaches were considered.

Results: Phytosomes, deformable vesicles, lipid nanoparticles, and self-nanoemulsifying systems have been reported to increase delivery of flavonoids, curcuminoids, and terpenoids with reported bioavailability gains of several-fold in individual mostly preclinical studies. Possibilities of targeted and multifunctional delivery of nanoparticles synthesized with green methods and chromatographic fingerprinting, marker standardization, DNA barcoding, artificial intelligence, and network pharmacology approaches were discussed.

Conclusion: Green extraction, nanoengineering, standardization, safety evaluation, and computational approaches may help in developing safe and effective next-generation herbal nanomedicines.

1. Introduction

Herbal medicines play a major role in health care for a large part of the world's population. The World Health Organization (WHO) traditional-medicine strategy encourages the integration, regulation, and evidence-based use of such medicines within national health systems (World Health Organization, 2013). Herbal medicine is valued for more than its cultural importance and low cost. Many standardized plant extracts have contributed to the structures of current small-molecule drugs. Interest in evidence-based phytotherapy has also grown because consumers are worried about synthetic drugs and their side effects (Patwardhan *et al.*, 2004). However, the wider use of herbal products has raised questions about their safety and standardization. It has shown that "natural" does not always mean "safe" (Ekor, 2014). The scale of this activity is large. Industry market-research estimates for the global herbal medicine market in 2025 range from about USD 85 billion to USD 270 billion, depending on scope and methodology. Most estimates project annual growth, from the high single digits to double digits, through the early 2030s. These reports often describe nanocarrier-based reformulation of existing botanicals, which is frequently cited by these reports as an emerging growth segment. Independent verification of any single figure is beyond the scope of this narrative review.

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Another major issue concerns pharmacokinetics rather than safety. Many phytochemicals show promise as antioxidant, anti-inflammatory, antimicrobial, and anticancer agents. Examples include curcuminoids, flavonoid aglycones, terpenoid lactones, saponins, and some alkaloids. However, they often have poor aqueous solubility and are unstable in the acidic conditions of the stomach. Many are also substrates of efflux transporters and undergo extensive conjugation during first-pass metabolism in the liver. As a result, a compound may be highly active in an in vitro cell experiment but much less active in vivo after oral administration and metabolism (Kesarwani *et al.*, 2013). Curcumin is a good example. It has been studied extensively, but its bioavailability is low because of rapid glucuronidation and sulfation and poor intestinal uptake (Anand *et al.*, 2010).

In this review, Herbal Drug Technology (HDT) means the deliberate redesign of the delivery vehicle, rather than the molecular structure, of a standardized plant component or extract. Pharmaceutical nanotechnology is used for this purpose to overcome one or more of the pharmacokinetic limitations described above (Bilia *et al.*, 2017). The review considers whole standardized extracts, standardized phytochemical fractions, and single isolated phytoconstituents together because all three share the same nanocarrier engineering literature. Where the difference affects the interpretation of a finding, it is stated in the relevant subsection. HDT lies at the interface of three formerly separate sciences. Phytochemistry provides the standardized active agent. Pharmaceutics provides the carrier engineering. Nanotoxicology and regulatory science, which are increasingly important, decide whether a new formulation can reach clinical practice (Kumar *et al.*, 2020). Over the last decade and a half, a diverse range of carriers has emerged. These include phytosomes, liposomes, niosomes, transferosomes, ethosomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, self-nanoemulsifying systems, chitosan and PLGA nanoparticles, green-synthesized metallic nanoparticles, and microsponge/nanosponge systems (Rahman *et al.*, 2020).

Two factors motivated this review. First, there are many excellent reviews of individual carrier types. However, few bring these platforms together in one review that helps researchers choose between them. Second, standardization, nanotoxicological safety, the regulatory pathway, and artificial intelligence-assisted formulation design are often covered in specialist literature. This literature rarely connects with the main delivery-system literature. Yet all of these points decide whether a laboratory-scale formulation will ever become a real medicine for patients (Chanda & Rakholiya, 2011). The review therefore has four aims. The first is to give an overview of the green extraction technologies that provide the standardized phytoconstituents on which any nanoformulation depends. The second is to compare vesicular, lipidic, emulsified, polymeric, metallic, and porous-polymer nanocarrier platforms against a consistent set of criteria. These are composition, principal route(s) of administration, reported bioavailability or pharmacokinetic gain, efficacy signal, safety data, level of evidence (in vitro, animal, human pharmacokinetic, or clinical), and regulatory/translational maturity. The comparison also covers their niche in ocular, nasal, buccal, and pulmonary delivery. The third is to describe the tools and procedures used to ensure the quality and safety of the products, including the key quality control parameters at the raw material, formulation, and product levels. The fourth is to assess the growing contribution of artificial intelligence and network pharmacology to rational herbal nanoformulation design.

2. Materials and Methods

This article was prepared as a structured narrative review and not a systematic review. The delivery platforms differ widely, and the primary literature is varied (formulation studies, mechanisms, pharmacopoeia, and regulatory guidance). Peer-reviewed articles, book chapters, and regulatory documents published between 1 January 2000, and 30 June 2026 (final search date) were from the PubMed, ScienceDirect, Scopus, Web of Science, and Google Scholar databases. More than 70% of the primary studies cited were published from 2015 onward. This reflects the recent growth of nanocarrier formulation work. Sources published before 2015 were kept mainly for foundational platform technologies (e.g., phytosome and liposome chemistry) and are identified as such in the relevant subsections. Regulatory documents were identified separately by searching the official websites of the World Health Organization (WHO), the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), the Indian Pharmacopoeia Commission (IPC), and the Ministry of AYUSH, Government of India. The search used the names of the relevant guidance instruments (e.g., 'nanomaterial-containing drug product guidance' and 'reflection paper nanotechnology medicinal products'). These documents are listed with their identifiers in Section 3.10.

Search keywords were combined by means of Boolean operators (AND/OR) within the following groups: (a) extraction—green extraction, supercritical fluid extraction, ultrasound/microwave-assisted extraction, subcritical water extraction; (b) vesicular vehicles—phytosome, liposome, niosome, transferosome, ethosome; (c) lipid and emulsified systems—solid lipid nanoparticle, nanostructured lipid carrier, nanoemulsion, self-nanoemulsifying drug

delivery system; (d) polymeric/metallic systems—chitosan nanoparticle, PLGA nanoparticle, green synthesis silver/gold nanoparticle; (e) porous and fibrous systems—microsponge, nanosponge, electrospun nanofiber, 3D-printed microneedle; (f) specialized routes—ocular, intranasal, buccal, pulmonary herbal delivery; (g) quality and safety—HPTLC/HPLC herbal fingerprinting, WHO herbal quality guidelines, DNA barcoding authentication, nanotoxicology, AYUSH pharmacovigilance; and (h) computational methods—artificial intelligence, machine learning, network pharmacology, herbal medicine. The same eight term groups were applied in all five bibliographic databases. Database-appropriate syntax was used: Medical Subject Headings (MeSH) terms in PubMed and free text with truncation in the other databases. The complete search string set and the last-search date for each database are summarized in Table 1.

Articles were included if they reported original formulations/characterizations, systematic reviews of a named delivery system, book-chapter treatments of a delivery platform, or regulatory guidance for a delivery system. This eligibility statement, the methods description of sources, and the abstract are consistent. All three describe peer-reviewed articles, book chapters, and regulatory/quality-agency documents as the three source types searched. Abstracts without access to data, articles not published in English, and studies on purely synthetic active agents were omitted from this search. Exceptions were made when such sources were essential for methodological background or historical perspective, or when a synthetic comparator was needed to illustrate a delivery-platform mechanism. Such comparators are explicitly flagged as non-herbal wherever they appear in the tables. For each eligible source, the delivery platform, phytoconstituent(s), formulation/characterization method, principal reported outcome, and level of evidence (in vitro, ex vivo, animal, human pharmacokinetic/clinical, or regulatory) were extracted into a structured spreadsheet. The findings were then synthesized narratively by platform (Sections 3.2–3.7) and by cross-cutting theme (Sections 3.8–3.13), rather than pooled quantitatively. The reference lists of selected review articles were also searched manually to find additional original research articles that the electronic search had missed. This is a narrative and not a systematic review. Formal Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting and risk-of-bias scoring were therefore not applicable and were not carried out. This is an inherent limitation of the narrative-review design. The review does not claim complete coverage of every platform-specific study. It offers only a representative synthesis of the literature identified through the search strategy above.

Table 1: Search Strategy Summary

Database/Source	**Last Search**
PubMed (MeSH + free-text, groups a–h)	30-Jun-26
ScienceDirect (free text, truncated)	30-Jun-26
Scopus (TITLE-ABS-KEY)	30-Jun-26
Web of Science (Topic search)	30-Jun-26
Google Scholar (hand-search)	30-Jun-26
WHO / FDA / EMA / IPC / AYUSH sites	30-Jun-26

3. Results and Discussion

3.1. Green Extraction as the Upstream Platform of Herbal Drug Technology

No nanocarrier, however sophisticated, can correct the problems of a raw extract whose characteristics and preparation were poorly controlled. Extraction technology should therefore be regarded as the basis of herbal drug technology and not as a preliminary step. Traditional techniques such as maceration, Soxhlet extraction, and hydro-distillation are still widely used. However, they are laborious, energy-consuming, and slow, and they may degrade heat-sensitive phenolics and volatiles (Zhang *et al.*, 2018). These problems led to the development of "green" extraction technologies. These technologies strive for the shortest possible processing time, reduction or removal of dangerous organic solvents, and protection of heat-sensitive materials (Usman *et al.*, 2023).

3.1.1. Supercritical and Subcritical Fluid Extraction

Supercritical fluid extraction usually uses carbon dioxide in the supercritical phase. The fluid combines solvating power with high diffusivity. It therefore extracts lipophilic and volatile compounds efficiently and cleanly. Changing the temperature and pressure alters the polarity of the fluid and allows selective extraction (Da Silva *et al.*, 2016). The method is especially suitable for essential oils and other oxidizable compounds because it uses no toxic solvent and runs under mild conditions. These properties are useful when the extracted compounds will be used in nanodispersions (Uwineza & Waśkiewicz, 2020). Subcritical (pressurized hot) water extraction is an alternative. Water is used as the

solvent in its subcritical form without the addition of any chemicals (Nastić *et al*., 2018).

3.1.2. Ultrasonic and Microwave-Assisted Extraction

Ultrasound technology uses acoustic cavitation to break the cells of the plant tissue and to promote solvent penetration. After just a few minutes, it has been proved that ultrasound technology can increase the effectiveness of the extraction of polyphenols and flavonoids compared to maceration (Islam *et al*., 2023). Dielectric heating used in microwave-assisted extraction helps to rapidly raise the temperature of the plant material. In case of proper optimization, microwave-assisted extraction has been found to be as efficient as or even more efficient than ultrasound extraction regarding the phenolic extraction, as seen from experiments performed on the pomegranate peel (Kaderides *et al*., 2019). Techniques that combine methods like ultrasound-assisted supercritical extraction have been shown to give better results.

Whichever extraction technique is chosen, the phytoconstituent content of the extract determines the loading capacity, size control, and biological efficacy of any later nanoformulation. The extraction process should therefore be controlled as carefully as the nanocarrier synthesis itself.

Quality Control of the Extract: The extract should be checked before it is used for nanoformulation. The main parameters are extraction yield, moisture content (loss on drying), total ash and acid-insoluble ash, marker-compound content, and the chromatographic fingerprint (HPTLC or HPLC). Residual solvents must be within pharmacopoeial limits. This is especially important for conventional organic-solvent extracts. Heavy metals, pesticide residues, aflatoxins, and microbial load must also be controlled (Indian Pharmacopoeia Commission, 2022; World Health Organization, 2011). Supercritical CO_2 and subcritical water extraction leave little or no organic solvent residue, which simplifies this control. Acceptance limits for these parameters should be fixed before formulation so that the final product can be reproduced from batch to batch. The tests are described in Section 3.9.

3.2. Vesicular Nanocarrier Platforms

Table 2 compares the platforms in terms of composition, advantages, limitations, illustrative phytoconstituents, and level of evidence. The principal nanocarrier architectures discussed in this section and in Sections 3.3–3.7 are shown schematically in Figure 1.

Figure 1 helps to explain how these carriers differ. In the phytosome, the phytoconstituent is bound to the polar head groups of phospholipid molecules as a complex. It is not simply trapped inside a carrier. In liposomes, niosomes, and transferosomes, one or more bilayers enclose an aqueous core. Hydrophilic compounds are held in the core and lipophilic compounds in the bilayer. In SLNs, NLCs, and polymeric nanoparticles, the active is dispersed in a solid or semi-solid matrix. In nanoemulsions and SNEDDS, it is dissolved in oil droplets. Green-synthesized metallic nanoparticles have a metal core with phytochemicals adsorbed on the surface as a capping layer. Microsponges and nanosponges have a porous network that holds the active in many small cavities. These structural differences explain many of the differences in loading capacity, release behavior, and stability discussed below.

3.2.1. Phytosomes

Phytosomes are nanoscale drug delivery systems (Figure 1). They are made by combining standardized phytochemicals with phosphatidylcholine or its analogues in a non-aqueous solvent. The phytochemicals are typically highly polar compounds, such as flavonoids, tannins, and some terpenoids. The two components form a supramolecular complex held together by hydrogen bonds (Bombardelli, 1991). This complexation turns the poorly permeable polyphenol into a more lipophilic form that can cross the intestinal epithelium. The effect has been reported, mainly in preclinical and small human pharmacokinetic studies, for silymarin, curcumin, quercetin, and Ginkgo biloba flavonoid complexes compared with the free extract (Kidd, 2009; Kumar *et al*., 2020; Kumar *et al*., 2020). Small human pharmacokinetic studies compared curcuminoid–phospholipid complexes with unformulated curcuminoid mixtures. They reported several-fold higher absorption with the complexes (Cuomo *et al*., 2011; Jager *et al*., 2014). Representative pharmacokinetic outcomes for these and other platforms are summarized in Table 3. These values come from different species, doses, and study designs. They are therefore not directly comparable and should not be ranked against each other.

Phytosomes can be prepared by solvent complexation with rotary evaporation, by anti-solvent precipitation, or, more recently, by supercritical-fluid-based complexation. Differential scanning calorimetry, FTIR, and ^{1}H-NMR are used to confirm true hydrogen bonding between the phospholipid and the phytoconstituent. They also distinguish it from simple co-precipitation (Gaikwad *et al*., 2021; Semalty *et al*., 2010). Besides oral use, phytosomes have been used in topical and wound care. Moringa oleifera leaf extract, for example, has been formulated as a phytophospholipid complex for potential use in wound dressings (Lim *et al*., 2019). The technique has several limitations. The phospholipid-to-phytoconstituent ratio can vary between batches. It is difficult to prove true molecular complexation at an industrial scale. Pharmaceutical-grade

phospholipid is also relatively expensive. Box–Behnken response surface methodology has been used to design antidiabetic phytosome formulations. This reflects a growing use of design of experiments instead of trial-and-error optimization (Rathee & Kamboj, 2018).

Quality Control of Phytosomes: The key parameters are complexation efficiency (the percentage of the phytoconstituent actually bound to phospholipid), drug content, particle size, polydispersity index (PDI), and zeta potential. The phospholipid-to-phytoconstituent ratio must be fixed and checked in every batch, because variation in this ratio is the main cause of batch inconsistency. Complexation is confirmed by DSC, FTIR, and ^{1}H-NMR, as described above. Water content, residual organic solvent from the preparation step, and the release profile are also checked. Stability is assessed by following drug content and complexation over time (Section 3.9).

3.2.2. Liposomes

Liposomes are phospholipid vesicles with a single bilayer (unilamellar) or several concentric bilayers (multilamellar) (Figure 1). They can carry a hydrophilic component in the aqueous core and a lipophilic component in the bilayer at the same time. This dual loading makes them a well-known reference platform for delivering herbal extracts (Söğüt *et al*., 2021). The phospholipid bilayer also resembles the cell membrane. This allows liposomes to interact with biological membranes more effectively than non-lipid carriers (Sercombe *et al*., 2015). Long-circulating, polyethylene glycol (PEG)-modified (PEGylated) liposomes carrying curcumin and a synthetic cytotoxic drug have been developed using a quality-by-design approach. This shows that current liposomal HDT formulations are mostly designed within a defined design space and not by trial and error (Tefas *et al*., 2017). Liposomes have also been functionalized with targeting ligands. One example is theranostic liposomes coated with D-α-tocopheryl polyethylene glycol succinate (TPGS) for co-delivery of a cytotoxic agent and an imaging probe. This shows that the platform can be adapted to combination and image-guided therapy, which is also relevant to the co-delivery of phytoconstituents (Muthu *et al*., 2012). The main translational limitation of liposomes is physical instability during storage. This includes aggregation, vesicle fusion, and phospholipid oxidation. It has stimulated interest in proliposomes, which are dry powder precursors reconstituted just before use (Singh *et al*., 2019).

Quality Control of Liposomes: The important parameters are vesicle size, PDI, zeta potential, lamellarity, entrapment efficiency, and drug content. Vesicle size is usually measured by dynamic light scattering (DLS) and shape by transmission electron microscopy (TEM). Entrapment efficiency is determined by separating the free from the entrapped drug (ultracentrifugation, dialysis, or gel filtration) and assaying both fractions by HPLC or UV spectroscopy. Phospholipid quality also matters, so oxidation (peroxide value) and hydrolysis (lysophospholipid content) should be monitored during storage. Other tests include in vitro release, leakage of the entrapped active, and pH. Sterility and endotoxin limits apply to injectable or ocular products. A PDI below about 0.3 and an absolute zeta potential above about 30 mV are commonly accepted as signs of a homogeneous and stable dispersion. Acceptance limits should still be justified for each product.

3.2.3. Niosomes

In liposomes, the bilayer is made of phospholipid. In niosomes, it is made of a non-ionic surfactant, usually reinforced with cholesterol (Figure 1). This gives an inexpensive and chemically more stable vesicular carrier that can entrap both hydrophilic and lipophilic actives. These "phytoniosomes" have been reported to encapsulate plant alkaloids, essential oils, and flavonoid aglycones. Chitosan glutamate-coated niosomes are also being studied for nose-to-brain delivery. Their mucoadhesive properties prolong their stay in the nasal cavity (Rinaldi *et al*., 2018). Compared with liposomes, niosomes are easier to prepare in large quantities and are more shelf-stable. However, the irritant nature of the surfactant itself may be a concern (Pandey *et al*., 2021).

3.2.4. Transferosomes and Ethosomes

Transferosomes add an edge-activator surfactant to the bilayer of an otherwise normal phospholipid vesicle (Figure 1). This makes the vesicle ultradeformable. It can squeeze between the cells of the intact stratum corneum, following the transepidermal hydration gradient, without breaking apart (Bnyan *et al*., 2019). Transferosomal gels of actives such as piroxicam and of phytosomes penetrated the skin barrier significantly better than conventional liposomes or simple topical preparations. This supports the mechanism behind adding an edge activator. Ethosomes pursue the same goal in a different way. They contain large amounts of ethanol, which fluidizes the vesicle membrane and disorders the lipids of the stratum corneum. This improves the penetration of terpenoid and flavonoid-containing extracts compared with control vesicles that do not contain ethanol. Poor storage stability is a problem for all vesicles. The particular benefits of each subclass should be considered when choosing a delivery system. These are low cost for niosomes, deformability for transferosomes, and enhanced skin penetration for ethosomes (Karim *et al*., 2016).

Quality Control of Niosomes: transferosomes and ethosomes. As for liposomes, vesicle size, PDI, zeta potential, and entrapment efficiency are measured for each batch. Additional parameters depend on the vesicle type. For niosomes, the surfactant-to-cholesterol ratio and the surfactant grade are controlled, and surfactant irritancy is considered. For transferosomes, deformability (extrudability through a membrane of fixed pore size) is a key functional test. For ethosomes, the ethanol content is controlled. Topical products are also tested for pH, viscosity, spreadability, ex vivo skin permeation and drug deposition in the skin (Franz diffusion cell), and for skin irritation. Storage stability is checked by following vesicle size, drug leakage, and drug content over time (Section 3.9).

3.3. Lipid-based Nanoparticulate System: Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC)

In solid lipid nanoparticles (SLNs), solid lipids replace the liquid oils used in the oily phase of a conventional emulsion (Figure 1). The solid lipids form a physiological and biodegradable matrix that is stabilized by a surfactant system. SLNs therefore combine the advantages of lipid carriers and polymeric nanoparticles. In oral delivery of phytobioactives, the rigid solid lipid matrix protects unstable compounds from enzymatic breakdown and pH changes in the gastrointestinal tract (Ghasemiyeh & Mohammadi-Samani, 2018).

A major disadvantage of first-generation SLNs is the gradual loss of the loaded drug. The matrix lipid slowly relaxes from a metastable form into a more ordered, thermodynamically stable crystalline state. This pushes the entrapped drug out of the matrix (Mei *et al.*, 2003). Nanostructured lipid carriers (NLCs) solve this problem by adding a liquid lipid to the matrix. This creates a deliberately imperfect crystal structure. It increases the loading capacity and significantly reduces drug expulsion during storage compared with first-generation SLNs. Both systems are widely used for topical and dermal delivery of essential oils, curcuminoids, and terpenoid extracts. They also hydrate the skin by forming a lipid layer, in addition to delivering the active through the skin. Current problems include the low loading efficiency of highly hydrophilic phytoconstituents and the need for high-pressure homogenization equipment to obtain a consistent particle size. Prolonged stability studies are also needed to follow polymorphic transformation.

Quality Control of SLNs and NLCs: The critical parameters are particle size, PDI, zeta potential, entrapment efficiency, drug loading, and drug content. The main stability problem is recrystallization of the lipid, so the physical state of the lipid matrix must be monitored. Differential scanning calorimetry and powder X-ray diffraction are used to follow crystallinity and polymorphic change. Particle size and drug expulsion are checked during storage. The grade of lipid and surfactant is controlled, and so is residual organic solvent when a solvent-based preparation method is used. A narrow size distribution (low PDI) should be shown for several batches to demonstrate that the homogenization process is reproducible. Topical products are also tested for pH, occlusion, and skin irritation.

3.4. Emulsified delivery systems: Nanoemulsions and Self-Nanoemulsifying Drug Delivery Systems

3.4.1. Nanoemulsions

Nanoemulsions are stabilized oil-in-water or water-in-oil dispersions with an average droplet diameter of less than 200 nm (Figure 1). They are made by high-energy techniques, such as high-pressure homogenization, microfluidization, and ultrasonication, or by low-energy techniques, such as phase inversion and spontaneous emulsification. Nanoemulsion droplets have a very large interfacial surface area compared with their volume. This significantly increases the dissolution rate and the mucosal or transdermal permeability of the lipophilic actives they carry, compared with a coarse emulsion or the raw oleoresin extract. Nanoemulsions have been used successfully in cosmeceutical, topical, and oral dosage forms. Examples in the literature include antileishmanial oleoresin nanoemulsions and polyherbal nanoemulsion gels for acne vulgaris. Both use plant-derived actives, such as garlic oil and manuka honey. In their review of nanoemulsions, Sutradhar and Amin noted that the size-dependent mechanisms that improve oral bioavailability and topical/transdermal permeation are similar. Principles learned from one route can therefore be applied directly to the other.

3.4.2. Self-Nanoemulsifying Drug Delivery Systems (SNEDDS)

Self-nanoemulsifying drug delivery systems (SNEDDS) extend the nanoemulsion concept to a pre-concentrate. This is an isotropic mixture of oil, surfactant, and co-surfactant. On dilution, and with the gentle agitation provided by gastrointestinal motility, it spontaneously forms a fine nanoemulsion. This avoids the dissolution-rate-limited absorption step that otherwise restricts the oral bioavailability of poorly soluble actives (Singh *et al.*, 2009). SNEDDS of curcumin increased peak plasma concentration and overall systemic exposure several-fold compared with a simple aqueous suspension. In rats, one such system raised peak plasma concentration by about 3.95-fold and bioavailability

by about 194% relative to a curcumin suspension (Nazari Vanani *et al.*, 2017). Comparable improvements have been reported for SNEDDS of andrographolide, sesamin, betulinic acid, and tetrandrine. Each was optimized using a pseudo-ternary phase diagram, which defines the region of spontaneous nanoemulsification for the oil–surfactant–co-surfactant combination used (Wang *et al.*, 2020; Bravo-Alfaro *et al.*, 2022). Polyherbal SNEDDS combine two plant extracts in a single self-emulsifying vehicle, for example, Begonia medicinalis and Moringa oleifera. They show that the platform is not limited to single-constituent systems (Asita *et al.*, 2024). Common concerns for nanoemulsions and SNEDDS include gastrointestinal irritation from high surfactant concentrations and the risk of drug precipitation if dilution goes beyond the nanoemulsification region defined by the phase diagram. Long-duration human pharmacokinetic data for herbal, as opposed to synthetic, actives are also still scarce.

Quality Control of Nanoemulsions and SNEDDS: For nanoemulsions, the main parameters are droplet size (below 200 nm), PDI, zeta potential, pH, viscosity, refractive index, electrical conductivity, and drug content. Physical stability is tested by centrifugation, heating–cooling cycles, and freeze–thaw cycles. Creaming, phase separation, droplet coalescence, and Ostwald ripening are looked for during storage. For SNEDDS, additional parameters are the self-emulsification time, the droplet size after dilution in water or in simulated gastric and intestinal fluids, and the percentage transmittance of the diluted system. Robustness to dilution and to pH change is also tested. Drug precipitation after dilution is checked, together with the thermodynamic stability and in vitro dissolution of the pre-concentrate. These systems contain high levels of surfactant, so the type and amount of surfactant and co-surfactant should be controlled and justified for safety.

3.5. Polymeric Nanoparticulate Systems

3.5.1. Chitosan-Based Nanoparticles

Chitosan is a cationic polysaccharide made by deacetylation of chitin (Figure 1). Chitosan nanoparticles form easily by mild aqueous ionic gelation, without the organic solvents used for most synthetic polymers (Panyam & Labhasetwar, 2003). The positive charge of chitosan gives mucoadhesion and temporarily opens the tight junctions between epithelial cells. This allows paracellular transport of the enclosed drug across the intestine or the nasal mucosa. In preclinical chemoprevention studies, curcumin–chitosan nanoparticles showed efficient cellular internalization and preferentially killed cancer cells rather than normal cells in vitro, without any change in the chemical structure of the drug (Anitha *et al.*, 2011).

3.5.2. PLGA and Hybrid Polymeric Nanoparticles

Poly(lactic-co-glycolic acid) (PLGA) is a biodegradable synthetic polymer with FDA approval precedent. Compared with chitosan, it gives more precisely controllable hydrolytic release. The release rate is determined mainly by the lactide-to-glycolide ratio and the molecular weight of the polymer (Chereddy *et al.*, 2016). Curcumin-loaded PLGA nanoparticles prepared by nanoprecipitation showed markedly higher oral bioavailability in rats than curcumin co-administered with piperine (Shaikh *et al.*, 2009). Modifying the PLGA surface with chitosan or PEG gives the particles "stealth" properties, which prolong their circulation time (Panyam & Labhasetwar, 2003). Ligand conjugation, for example with folate or galactosylated chitosan, extends the platform to tumor-selective delivery in cancer treatment. Optimization methods such as Box–Behnken design are also becoming routine in nanoparticle development (Yallapu *et al.*, 2012).

Quality Control of Polymeric Nanoparticles: Particle size, PDI, zeta potential, entrapment efficiency, drug loading, and in vitro release are the standard parameters. For chitosan, the degree of deacetylation and the molecular weight affect particle size, charge, and mucoadhesion. They must therefore be specified for each polymer batch. For PLGA, the lactide-to-glycolide ratio and the molecular weight control the release rate and are likewise specified. Residual organic solvents, for example from nanoprecipitation, are measured against pharmacopoeial limits. Residual surfactant or stabilizer (for example, polyvinyl alcohol) is also checked. Freeze-dried products are checked for redispersibility and residual moisture. Particle size, drug content, and release are followed in stability studies.

3.6. Green-Synthesized Metallic Nanoparticles

Green synthesis uses the plant extract itself, and not added chemical reagents, to reduce a metal salt precursor and to cap the surface of the resulting nanoparticle. It is most often used for silver and gold (Figure 1). This avoids the toxic reducing and capping agents of conventional chemical synthesis. The phytochemicals that reduce and cap the particles are typically polyphenols, flavonoids, and some proteins. They remain adsorbed on the nanoparticle surface after synthesis. They often contribute directly to biological activity and do not serve a purely structural role. Biogenic silver nanoparticles made from many leaf, seedcoat, and fruit extracts have shown consistent antimicrobial activity against multidrug-resistant bacterial and fungal clinical isolates. This is at least partly due to synergy between the metal core and the adsorbed capping phytochemicals (Vanlalveni *et al.*, 2021). Gold nanoparticles made under microwave-assisted green conditions and dual silver–gold systems made from

a single leaf extract have shown anticancer, antioxidant, and catalytic properties in addition to simple antimicrobial action. Broader reviews of medicinal-plant-mediated metal nanoparticle synthesis stress the variety of applications now being explored, from cancer therapy to environmental remediation (Sharma *et al.*, 2018). There are also unresolved concerns. Long-term biodistribution and clearance are incompletely characterized. Batch-to-batch variability arises from natural variation in the phytochemical content of the source extracts. Comparative toxicological data also suggest that biosynthesized and chemically synthesized nanoparticles of the same nominal composition are not necessarily equivalent in their safety profile (de Lima *et al.*, 2012).

Quality Control of Green-Synthesized Metallic Nanoparticles: Formation of the nanoparticles is first confirmed by UV–visible spectroscopy, which shows the surface plasmon resonance band. Size and size distribution are measured by DLS and TEM, and the crystalline structure by X-ray diffraction. FTIR is used to identify the phytochemicals on the surface, and zeta potential indicates colloidal stability. The metal content should be quantified, for example by atomic absorption spectroscopy or inductively coupled plasma–mass spectrometry, together with the amount of free (unreacted) metal ions. The capping layer comes from the extract, so the reproducibility of the extract (marker content and fingerprint) must be controlled. Each batch of nanoparticles should be compared with a reference batch. For biological use, limits for sterility, endotoxin, and residual metal ions are also relevant.

3.7. Microsponges, Nanosponges, and Next Generation Fibrous/3D-Printed Delivery Platforms

3.7.1. Microsponges and Nanosponges

Microsponges are porous, crosslinked polymeric microspheres, usually 10–25 micrometers in size (Figure 1). They can entrap up to about 50–60% w/w of the drug and release it in a programmable way, possibly in response to stimuli. They were first used to reduce skin irritation from highly potent topical drugs, such as benzoyl peroxide, without reducing their activity. Similar technology is now applied to herbal drugs. Curcumin microsponges for oral (capsule) and topical (gel) delivery showed better drug release and bioadhesion than free curcumin (Bhatia & Saini, 2018). Nanosponges, often built on cyclodextrin chemistry, scale this concept down to the nanoscale. They further increase the surface-area-related dissolution and are used for topical delivery of poorly soluble antifungal and herbal drugs.

3.7.2. Nanofibers, 3D Printing, and Microneedle Arrays

Electrospinning is used to make nanofiber scaffolds from natural biomacromolecules, such as collagen, keratin, and hyaluronic acid, or from biodegradable synthetic polymers, such as polylactic acid. Loaded with herb extracts, these scaffolds have been developed as wound dressings. They imitate the extracellular matrix, give physical support, and release phytochemicals continuously to promote wound healing. The newest technologies are three-dimensional printing methods. These include filament-based fused deposition modeling, semisolid extrusion printing, and, in particular, dissolvable or hydrogel-based microneedle arrays. They allow patient-specific dressings, controllable drug loading, and minimally invasive transdermal delivery of phytomolecules and nanofabricated herbal formulations (Patitucci *et al.*, 2024). Microneedle delivery of macromolecules and proteins was designed mainly for synthetic biologics. It is becoming more common for herbal peptide and protein active ingredients (Jamaledin *et al.*, 2020).

Quality Control of Microsponges, Nanofibers, and Microneedles: For microsponges, the parameters include production yield, particle size and size distribution, morphology (scanning electron microscopy), pore structure and surface area, drug loading, entrapment efficiency, and in vitro release. Residual solvent from the quasi-emulsion solvent diffusion method is also controlled. For electrospun nanofibers, important parameters are fiber diameter and uniformity, porosity, mechanical strength, swelling or moisture uptake, drug content, release profile, and sterility. For microneedles and 3D-printed products, needle dimensions, mechanical strength (insertion without breakage), drug content uniformity, dissolution time, skin penetration, and sterility are assessed. Wound dressings and microneedles contact broken or pierced skin, so biocompatibility and bioburden limits should be met.

3.8. Niche and Emerging Administration Routes for Herbal Nanoformulations

Oral and topical/transdermal delivery dominate the HDT literature. However, several less-studied routes offer clear advantages for particular therapeutic goals, and formulation interest in them is growing. Ocular delivery must overcome rapid nasolacrimal drainage and the tight corneal epithelial barrier. Nanoparticulate and in situ gelling systems have been used to prolong pre-corneal residence time and improve the ocular bioavailability of synthetic and, increasingly, phytoconstituent-based anti-inflammatory and antimicrobial actives (Achouri *et al.*, 2013). Intranasal delivery uses the rich blood supply and fairly permeable

epithelium of the nasal mucosa. It also allows direct nose-to-brain transport along the olfactory and trigeminal pathways, which bypasses the blood–brain barrier (BBB) entirely. Mucoadhesive niosomal and chitosan-based nanocarriers have been designed specifically to use this route for centrally acting herbal actives (Illum, 2003; Kisku *et al.*, 2024). Buccal and other oral-transmucosal routes avoid first-pass hepatic metabolism altogether, because the active is absorbed directly into the systemic circulation across the oral mucosa. This is particularly attractive for phytoconstituents such as curcuminoids, which are extensively metabolized on first hepatic pass (Patel *et al.*, 2011). Pulmonary delivery has been developed mostly for synthetic anti-tubercular and anti-inflammatory agents. It offers a large absorptive surface area and the possibility of direct macrophage targeting, which is relevant to respiratory infections. Inhalable herbal nanoparticulate systems are only beginning to explore this concept (Sharma *et al.*, 2001). For all four routes, the core HDT nanocarrier chemistries described in Sections 3.2–3.6 are being adapted rather than replaced. Mucoadhesive surface functionalization and precise particle-size control are the common formulation tools, whatever the anatomical target. The characteristics of each route and the nanocarriers typically applied are summarized in Table 4.

Quality Control for these Routes: Quality requirements depend on the site of administration. Ocular preparations must be sterile and free of visible particles. Their pH should be close to that of tears, and osmolality and viscosity must be controlled to avoid irritation and to prolong residence time. Intranasal formulations are checked for pH, viscosity, droplet or particle size, mucoadhesive strength, and, where relevant, ciliotoxicity. Buccal films and patches are tested for thickness, weight uniformity, surface pH, swelling, folding endurance, mucoadhesion, and drug release. Inhalable products are characterized by aerodynamic particle size, which determines the site of lung deposition, together with moisture content and emitted dose. For all four routes, particle size, PDI, zeta potential, drug content, and stability remain the core parameters (Section 3.9).

3.9. Standardization, Quality Control, and Analytical Fingerprinting

Herbal extracts contain many components. Their composition also varies with cultivar, growing area, harvesting period, and post-harvest practices. Standardization is therefore essential for herbal nanoformulations intended for clinical use (Indrayanto, 2022). The WHO guidance on quality control methods for herbal materials describes a step-by-step approach. It starts with authentication by macroscopic and microscopic examination. This is followed by non-specific tests, identification of markers, quantification of marker compounds, and chromatographic fingerprinting. Good Agricultural and Collection Practices (GACP) apply upstream, and Good Manufacturing Practices (GMP) apply downstream (World Health Organization, 2011). HPTLC is still the identity test most often required by official pharmacopoeial texts, such as the Indian Pharmacopoeia monographs of classical herbs like turmeric, ashwagandha, and giloy. HPLC and GC–MS fingerprints offer higher resolution and semiquantitative information about composition (Choudhary & Sekhon, 2011; Indian Pharmacopoeia Commission, 2022; Liang & Wang, 2011).

Multivariate chemometric analysis is becoming popular as a supplement to simple visual comparison of chromatograms. It includes similarity indices, partial least-squares discriminant analysis, and soft independent modeling of class analogy. These tools improve the discrimination between authentic material and look-alikes (Alaerts *et al.*, 2007). DNA barcoding is a useful sequence-based method of validation. It is especially valuable for plants that look alike or have been heavily processed, where chromatographic separation is difficult (Techen *et al.*, 2014; Raclariu *et al.*, 2018). Adulteration studies of Chinese and Ayurvedic herbal supplements show clearly that a multimodal approach to validation is necessary and not optional. Standardization should cover not only the extract but also the final nanoparticle formulation. The parameters include particle size, polydispersity index, zeta potential, entrapment and encapsulation efficiency, and in vitro release profile. The principal analytical and characterization techniques used for this purpose are summarized in Table 5.

Quality Control of Herbal Nanoformulations Works at Three Levels: At the raw-material level, pharmacopoeial and WHO parameters are used to confirm the identity, purity, and strength of the plant material or extract. These include foreign matter, moisture content (loss on drying), total ash and acid-insoluble ash, extractive values, and marker content. Limits for heavy metals, pesticide residues, aflatoxins, and microbial load must also be met (Indian Pharmacopoeia Commission, 2022; World Health Organization, 2011). Residual solvents from extraction and from nanoparticle preparation must be controlled as well. At the formulation level, the critical quality attributes are particle size, polydispersity index, zeta potential, drug content (assay), drug loading, entrapment efficiency, morphology, and in vitro release. Depending on the dosage form and the route of administration, pH, viscosity, osmolality, sterility, and bacterial endotoxin limits are added, for example, for ocular or parenteral products (Indrayanto, 2022). At the product level, ICH-aligned stability studies establish the shelf life. They follow these attributes, together with marker content, over time under defined storage conditions (International Council for Harmonisation, 2003). Acceptance ranges for

each parameter should be justified for the specific extract and route of administration. In this way, batch-to-batch reproducibility is demonstrated and not assumed.

Interpreting Quality Control Parameters: Some commonly used reference values help to interpret these parameters. A PDI below about 0.3 is generally taken to indicate a reasonably uniform population for lipid-based carriers. An absolute zeta potential above about 30 mV is commonly associated with good electrostatic stability, although sterically stabilized systems can be stable at lower values. Entrapment efficiency is the amount of active entrapped divided by the total amount added, expressed as a percentage. Drug loading is the amount of active per unit weight of carrier. All assays should use validated analytical methods, with specificity, linearity, accuracy, precision, and robustness demonstrated (Indrayanto, 2022). Under ICH Q1A(R2), long-term stability studies are usually run at 25°C/60% relative humidity (RH) or 30°C/65% RH, and accelerated studies at 40°C/75% RH (International Council for Harmonisation, 2003). The pharmacokinetic gains reported in Table 3 should be read together with these quality parameters. A formulation without defined and reproducible quality attributes cannot be compared fairly with another.

3.10. Regulatory Oversight and Nanotoxicological Safety

At present, herbal nanomedicines sit in an uneasy position between two regulatory regimes. Traditional/herbal medicine regulation is on one side, and nanomedicine regulation is on the other. Each is difficult in itself, and the two are poorly connected. In India, Ayurveda, Siddha, Unani, and Homeopathy (ASU&H) products under AYUSH regulation are covered by a national pharmacovigilance system. It identifies adverse events and complaints about product quality. This shows that herbal products are recognized to need the same post-market monitoring as conventional synthetic medicines, whether or not they are formulated as nanoparticles (Dias & Joshi, 2024; Ministry of AYUSH, 2018). Internationally, the US FDA and the European Medicines Agency have issued guidance or reflection papers on the physical and chemical characterization and risk assessment expected for nanopharmaceuticals (European Medicines Agency, 2006; US Food and Drug Administration, 2022). Stability-testing guidance aligned with ICH Q1A(R2) is being extended, by implication, to phytoformulations that use nanotechnology (International Council for Harmonisation, 2003). However, a harmonized regulatory regime for herbal nanomedicines has not yet been developed. This creates uncertainty for manufacturers. They must meet herbal quality requirements and nanomaterial safety requirements that were developed independently of each other (Foulkes *et al.*, 2020). The main regulatory and quality-control instruments relevant to herbal nanoformulations are summarized in Table 6.

The nanotoxicological risks of these products include the ability of nanoparticles to cross physiological barriers such as the BBB. They may also cause oxidative stress, inflammation, and genotoxicity and disturb the balance of the gut microbiome after ingestion. These effects are difficult to predict from the toxicology of the phytoconstituent. Dedicated preclinical evaluation of the products as nanoparticles is therefore needed, instead of relying on toxicity tests of the bulk extract (Oberdörster *et al.*, 2005). A systematic review of the regulation of nanomedicines in general found that the lack of internationally accepted standards for characterization and risk assessment is the biggest hurdle to timely and safe clinical translation. This is likely to apply equally to herbal nanomedicines (Havelikar *et al.*, 2024). Closing the regulatory gaps would probably need a coordinated framework. It would cover botanical identification and standardization, which belong to the traditional scope of herbal products, and nanoscale physicochemical and toxicological evaluation, which belong to the scope of nanomedicine.

Quality Control and Safety: Quality control parameters also serve safety purposes. Particle size, size distribution, surface charge, and surface chemistry should be reported for each batch, because they influence biodistribution and toxicity. Endotoxin and sterility testing are needed for products given by injection or to the eye. Limits for toxic heavy metals and residual solvents protect against toxicity from contaminants. In vitro cytotoxicity and hemolysis tests and, where appropriate, in vivo acute and repeated-dose toxicity studies of the final nanoformulation should be added to the characterization data (Section 3.9).

3.11. Patents, Commercialized Products, and Human Efficacy Evidence

The most developed commercial application of HDT vesicles is phytosome technology. It goes back to early patent work on phospholipid-based delivery of cosmetic and pharmaceutical active ingredients. It is now used in several marketed products based on standardized extract complexes of silymarin, ginkgo flavonoids, and curcuminoids (Bombardelli, 1991). Comparative human pharmacokinetic studies evaluated phospholipid-complexed versus unformulated curcuminoid mixtures. They showed marked increases in plasma exposure. This is one of the few examples of human pharmacokinetic evaluation of HDT carriers at the nanocarrier level (Kidd, 2009; Jager *et al.*, 2014). Apart from phytosomes, most of the other technologies presented in this review remain mainly

at the preclinical or early translational stage for herbal (rather than synthetic) active ingredients. These include SLNs/NLCs, nanoemulsions, SNEDDS, and polymeric and metallic nanoparticles. Efficacy and pharmacokinetic enhancement are reasonably well supported in preclinical models, but human data are limited (Bonifácio *et al.*, 2014). Representative patented platforms and clinically evaluated formulations, together with the type of evidence behind each, are listed in Table 7. For marketed products, reproducible quality control is what links the clinical findings to a defined product. This includes a standardized extract, a defined complex ratio, particle size data, and stability data.

3.12. Artificial Intelligence and Network Pharmacology in Herbal Drug Formulation

Herbal formulations are multicomponent and multitarget agents. This has always made mechanistic study and rational design harder than for single-molecule synthetic drugs. Network pharmacology and machine learning are now addressing this problem (Hopkins, 2008). Network pharmacology builds an interaction network between compounds, targets, and pathways from curated herbal chemical databases, such as the Traditional Chinese Medicine Systems Pharmacology Database. It is used to prioritize the phytoconstituents responsible for the therapeutic effects of the formulation before expensive wet-lab validation (Shao *et al.*, 2025). Machine learning techniques range from Support Vector Machines to random forests and graph neural networks. They have been used in herb screening, drug–target interaction prediction, and ADMET modeling of phytoconstituents.

In HDT, these computational methods are increasingly used not only to select bioactive compounds but also to design their nanoformulations. For example, they can predict which combinations of phytoconstituent and excipient give stable, high loading nanosystems. However, such prediction and its experimental verification are still being developed. As the two bodies of literature merge, AI-assisted screening may become an increasingly fast tool for optimizing herbal nanoformulations. This holds only if the predictions are based on experimentally proven physicochemical and pharmacokinetic results for the selected systems. Quality control data from well-characterized batches, such as particle size, entrapment efficiency, and stability results, are the natural training and validation data for such models.

3.13. Problems and Future Perspectives

3.13.1. Discussion: Cross-Platform Synthesis and Level of Evidence

Sections 3.1–3.12 are mainly descriptive. The interpretation that follows is offered separately and explicitly. The reviewed platforms differ greatly in their level of evidence. Treating them as interchangeable would overstate their comparative clinical readiness. Phytosomes are the only platform with decades of human pharmacokinetic data behind named commercial products (silymarin, ginkgo flavonoids, curcuminoids) (Bombardelli, 1991; Kidd, 2009; Jager *et al.*, 2014). They are therefore the only platform that can be considered clinically and commercially mature. SNEDDS and nanoemulsion formulations of curcumin, sesamin, and betulinic acid have reasonably strong preclinical pharmacokinetic evidence and, in some cases, early in vivo pharmacodynamic evidence (Asita *et al.*, 2024; Nazari Vanani *et al.*, 2017; Singh *et al.*, 2009). However, published human pharmacokinetic data for herbal (as opposed to synthetic) actives in these platforms remain scarce. Chitosan and PLGA nanoparticles, green-synthesized metallic nanoparticles, microsponges/nanosponges, and the nanofiber/3D-printed platforms are currently supported almost entirely by in vitro and animal (preclinical) data (Anitha *et al.*, 2011; Bhatia & Saini, 2018; Jamaledin *et al.*, 2020; Sharma *et al.*, 2018; Vanlalveni *et al.*, 2021). To our knowledge, none has reached a marketed herbal nanomedicine product or completed human clinical evaluation. The gradient is human clinical (phytosomes), then preclinical with some in vivo PK data (SNEDDS/nanoemulsions), then in vitro/animal-only (the remaining platforms). It is summarized in the Level of Evidence column added to Table 2. It should be kept in view whenever this review describes different platforms in similar terms. Similar descriptions should not be read as similar clinical maturity.

Two translational barriers affect nearly every platform discussed above and deserve direct comment. The first is scale-up. Laboratory batches are typically of milliliter to gram scale. Pilot or industrial production introduces process variables. These include the throughput of high-pressure homogenization or microfluidization, batch-to-batch heat transfer during solvent removal, and the effect of shear history on vesicle or particle size distribution. These variables are rarely reported in the primary literature reviewed here. A formulation that is optimal at bench scale therefore cannot be assumed to keep the same particle size, entrapment efficiency, or release profile when it is manufactured at scale (Indrayanto, 2022). Critical process parameters and in-process controls should be defined to close this gap. Examples are homogenization pressure and cycles, temperature, and stirring speed, with in-process particle-size checks. The second recurring gap is long-term storage stability. Physical instability includes vesicle aggregation, fusion, Ostwald ripening in nanoemulsions, and lipid polymorphic transition in SLNs. Chemical instability includes phospholipid oxidation and phytoconstituent degradation. Sections 3.2–3.5 describe these problems only

qualitatively. Few of the cited studies report ICH-aligned long-term (12- or 24-month) stability data under real-time storage conditions. Most use only short accelerated-stability windows. Proliposomes and other dry-powder-precursor strategies partly address this for vesicular systems (Singh *et al*., 2019). They have not been systematically extended to the other platforms reviewed here. Scale-up robustness and long-term storage stability should both be treated as standing translational risks and not as solved problems for every platform except phytosomes.

Some problems are common to all the platforms reviewed above. First, scaling up herbal nanocarriers is harder than scaling up single-molecule synthetic nanocarriers, because the active ingredient is inherently variable. A nanocarrier designed for one extract may behave differently with another, unless the standardized process (see Section 3.9) is carefully controlled (Indrayanto, 2022). Second, scientific support is quite unequal across platforms. Human pharmacokinetics have been studied thoroughly for phytosomes over several decades. SNEDDS, polymer-based and metallic nanoparticles have a relatively strong scientific basis at the preclinical stage but lack clinical evidence. This gap must be filled before such platforms can be regarded as clinically mature and not just technologically promising (Shao *et al*., 2025). Finally, studies on the nanotoxicity of herbal nanocarriers are lacking. There is also no regulatory framework that takes into account both herbal quality and nanosafety (Foulkes *et al*., 2020; Havelikar *et al*., 2024).

A further common problem is the lack of agreed quality control specifications for herbal nanoformulations. Few studies report the same set of parameters, and acceptance limits are rarely justified. A minimum reporting set would make studies comparable. It would include the marker content and fingerprint of the extract, particle size, PDI, zeta potential, entrapment efficiency, drug content, in vitro release, contaminant limits, and ICH-aligned stability data (Table 5).

Three main trends are likely to shape the next wave of HDT. First, combining green extraction with in-line chromatography will reduce batch-to-batch variation. This will make later nanoformulations easier for researchers to reproduce. Second, wider use of quality-by-design and design-of-experiments approaches, as in some of the formulation studies cited here, will make the optimization and characterization of the critical quality attributes of nanocarriers more uniform (Rathee & Kamboj, 2018; Tefas *et al*., 2017). Third, closer collaboration between formulators and network pharmacology scientists may shorten development time. This requires that hypotheses generated by artificial intelligence remain a tool for prioritization and do not replace the necessary experimental and regulatory validation of the technologies under development.

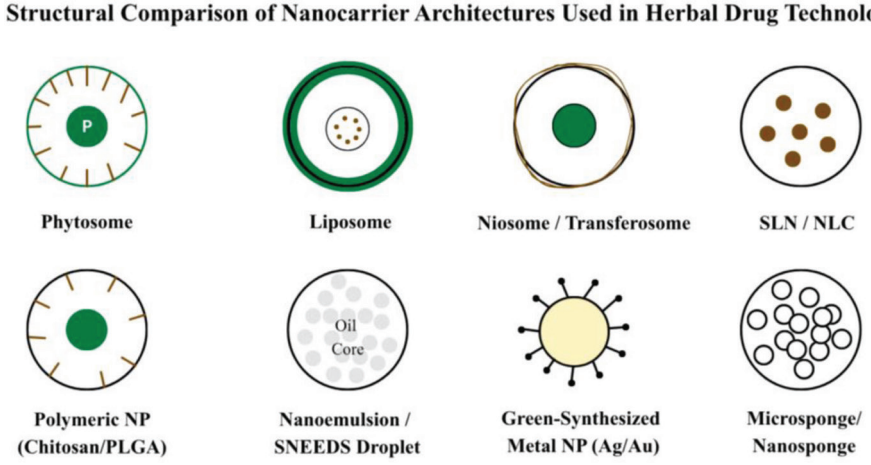


Figure 1: Schematic Structural Comparison of the Principal Nanocarrier Architectures

Table 2: Comparative Overview of Major Nanocarrier Platforms used in Herbal Drug Technology

Nanocarrier Platform	Representative Composition	Key Advantages	Principal Limitations	Illustrative Phytoconstituents
Phytosomes	Phytoconstituent–phospholipid (phosphatidylcholine) complex	Marked oral bioavailability gain; amphiphilic character aids membrane transit; some clinical PK data available	Batch-to-batch stoichiometric variability; difficult to confirm true complexation at scale	Silymarin, curcumin, quercetin, ginkgo flavonoids. Level of evidence: Human pharmacokinetic/clinical data available (mature).

Liposomes	Phospholipid bilayer vesicles (uni-/ multilamellar)	Co-encapsulates hydrophilic and lipophilic actives; membrane-mimicking structure	Physical/chemical instability on storage; scale-up cost	Green tea catechins, curcumin, resveratrol. Level of evidence: Preclinical (in vitro/animal); limited human PK data.
Niosomes	Non-ionic surfactant/ cholesterol bilayer vesicles	Lower-cost surfactants; improved chemical stability over liposomes	Surfactant-related irritation at higher concentration	Plant alkaloids, essential oils, flavonoid aglycones. Level of evidence: Preclinical (in vitro/animal) only.
Transferosomes / Ethosomes	Ultra-deformable lipid vesicles with edge activator/high ethanol	Enhanced transdermal flux via stratum corneum deformation/fluidization	Vesicle aggregation on storage; ethanol-related irritation risk	Terpenoid/flavonoid extracts. Level of evidence: Preclinical (in vitro/ animal/ex vivo skin) only. (Piroxicam is included in the underlying formulation literature only as a synthetic, non-herbal mechanistic comparator illustrating the transferosome edge-activator effect, not as an herbal-drug finding.)
Solid Lipid Nanoparticles (SLN)	Solid lipid matrix stabilized by surfactant	Biocompatible, scalable; sustained release; protects labile actives	Drug expulsion on lipid polymorphic transition	Curcuminoids, triptolide, essential oil terpenes. Level of evidence: Preclinical (in vitro/animal) only.
Nanostructured Lipid Carriers (NLC)	Solid + liquid lipid blended matrix	Higher loading, reduced expulsion vs SLN	More complex formulation optimization	Curcuminoids, essential oils for topical use. Level of evidence: Preclinical (in vitro/animal) only.
Nanoemulsions	Oil-surfactant-water isotropic/kinetically stable dispersion	Rapid dissolution/ permeation via high interfacial area	Surfactant-related irritation; limited thermodynamic stability	Curcumin, garlic oil, oleoresins, essential oils. Level of evidence: Preclinical, with some early human topical/oral data.
SNEDDS	Oil-surfactant-co-surfactant pre-concentrate	Spontaneous nanoemulsification in gastrointestinal (GI) fluid; bypasses dissolution step	Precipitation risk on dilution beyond phase-diagram region	Curcumin, andrographolide, sesamin, betulinic acid. Level of evidence: Preclinical with in vivo pharmacokinetic data; no dedicated human PK trials identified.
Chitosan Nanoparticles	Cationic polysaccharide matrix, ionic gelation	Mucoadhesive; opens tight junctions; mild aqueous synthesis	Moderate drug loading for some actives	Curcumin, catechins. Level of evidence: Preclinical (in vitro/animal) only.
PLGA / Hybrid Polymeric Nanoparticles	Biodegradable polyester matrix, optionally surface-functionalized	Tunable controlled release; ligand-targetable	Residual solvent; multistep synthesis	Curcumin, quercetin. Level of evidence: Preclinical (in vitro/animal) only.
Green-Synthesized Metallic Nanoparticles (Ag/Au)	Metal core reduced/ capped by plant phytochemicals	Eco-friendly synthesis; intrinsic antimicrobial/ anticancer activity	Biodistribution/ nanotoxicity uncertainty; batch variability	Reducing/capping agents from leaf, seedcoat, fruit extracts. Level of evidence: Preclinical (in vitro/animal); no human data identified.
Microsponges / Nanosponges	Porous cross-linked polymeric microspheres	Programmable release; reduced irritation; high payload	Limited to moderately lipophilic actives	Curcumin. Level of evidence: Preclinical (in vitro/animal) only. (Benzoyl peroxide is cited only as the synthetic comparator that established the microsponge irritation-reduction mechanism, not as an herbal-drug finding.)

Nanofibers / 3D-Printed Systems	Electrospun biomacromolecule or printed polymer scaffolds	Patient-specific geometry; sustained wound-site release	Manufacturing complexity; limited regulatory precedent	Olive leaf extract, wound-healing botanicals. Level of evidence: Preclinical (in vitro) only; no human data identified.

Note: Values are reproduced as reported in the cited sources and come from different species, doses and study designs, so they are not directly comparable between platforms. Only the curcuminoid phytosome entry is explicitly based on human comparative absorption studies; the other entries come from preclinical or review-level evidence and should not be read as evidence of clinical efficacy.

Each panel represents a simplified cross-section illustrating how the phytoconstituent (gold) is associated with its carrier matrix (green), highlighting the structural distinction between complexation-based (phytosome), bilayer (liposome, niosome/transferosome), matrix (SLN/NLC, polymeric nanoparticles), droplet (nanoemulsion/SNEDDS), core-shell (metallic nanoparticles) and porous (microsponge) architectures.

Table 3: Illustrative Oral Bioavailability/Pharmacokinetic Enhancement Data Reported for Representative Herbal Nanoformulations

Phytoconstituent	**Nanocarrier Platform**	**Reported Pharmacokinetic Outcome (vs. free/ unformulated active)**	**Reference**
Curcumin	SNEDDS	~3.95-fold increase in Cmax; ~194% enhancement in oral bioavailability	(Nazari Vanani *et al.*, 2017)
Curcuminoid mixture	Phytosome (phospholipid complex)	Several-fold increase in plasma AUC in human comparative absorption studies	(Jager *et al.*, 2014)
Sesamin	SNEDDS	Improved solubility and sustained plasma levels over a 12-week stability window	(Wang *et al.*, 2020)
Betulinic acid	SNEDDS (mucoadhesive)	SNEDDS improved betulinic-acid solubility and oral bioavailability, with nanoemulsion droplet size ~22–56 nm and high resistance to simulated GI digestion	(Bravo-Alfaro *et al.*, 2022)
Curcumin	Chitosan nanoparticles	Cellular uptake and selective cytotoxicity toward cancer cells in vitro	(Anitha *et al.*, 2011)
Curcumin	PLGA nanoparticles	Markedly higher oral bioavailability in rats	(Shaikh *et al.*, 2009)
Oleanolic acid	SNEDDS	Improved solubility enabling higher effective oral dose loading	(Singh *et al.*, 2009)
Silymarin	Phytosome	Improved hepatic bioavailability relative to unformulated extract	(Kidd, 2009)

Table 4: Representative Niche and Emerging Administration Routes for Herbal Nanoformulations

Route	**Anatomical/Physiological Feature Exploited**	**Nanocarrier Types Typically Applied**	**Illustrative Advantage/Citation**
Ocular	Corneal epithelial barrier; nasolacrimal drainage	Nanoparticulate suspensions, in situ gelling nanosystems	Prolonged pre-corneal residence, improved local bioavailability (Achouri *et al.*, 2013)
Intranasal/ Nose-to-Brain	Olfactory and trigeminal neural pathways bypassing the blood–brain barrier (BBB)	Mucoadhesive niosomes, chitosan nanoparticles	Direct central nervous system (CNS) access for centrally acting phytoconstituents (Illum, 2003; Kisku *et al.*, 2024)
Buccal/Oral-Transmucosal	Highly vascularized, permeable oral mucosa	Mucoadhesive films, nanoparticle-loaded patches	Avoids first-pass hepatic metabolism (Patel *et al.*, 2011)
Pulmonary	Large alveolar surface area; alveolar macrophage access	Inhalable nanoparticulate/ microparticulate systems	Direct respiratory-tract or macrophage targeting (Sharma *et al.*, 2001)

Table 5: Principal Analytical and Characterization Techniques used for Quality Control of Herbal Nanoformulations

Attribute Assessed	**Representative Technique(s)**	**Purpose in Herbal Nanoformulation QC/Citation**
Botanical Identity/ Authenticity	Macroscopic and microscopic examination, DNA barcoding	Confirms correct species and detects morphologically similar adulterants (World Health Organization, 2011; Techen *et al*., 2014; Raclariu *et al*., 2018)
Physicochemical Parameters of the Raw Material/Extract	Foreign matter, loss on drying (moisture), total ash, acid-insoluble ash, extractive values	Confirms purity and quality of the plant material or extract before nanoformulation (Indian Pharmacopoeia Commission, 2022; World Health Organization, 2011)
Contaminants and Residues	Heavy metals, pesticide residues, aflatoxins, microbial limits, residual solvents	Ensures safety of the raw material and finished product (World Health Organization, 2011)
Chemical Fingerprint	HPTLC, HPLC–DAD, GC–MS	Establishes a characteristic chromatographic profile for batch-to-batch comparison (Alaerts *et al*., 2007; Choudhary & Sekhon, 2011; Liang & Wang, 2011)
Marker Compound Quantification	HPLC, LC–MS/MS	Quantifies specific bioactive marker(s) against pharmacopoeial limits (Choudhary & Sekhon, 2011; Indian Pharmacopoeia Commission, 2022; Liang & Wang, 2011)
Particle Size/Polydispersity	Dynamic light scattering (DLS)	Confirms nanoscale dimensions and homogeneity of the carrier system (Indrayanto, 2022)
Surface Charge	Zeta potential measurement	Predicts colloidal stability and mucoadhesive/cellular interaction behaviour (Indrayanto, 2022)
Morphology	TEM, SEM, atomic force microscopy (AFM)	Visualizes vesicle/particle shape, surface texture, and structural integrity (Indrayanto, 2022)
Complexation/Interaction Confirmation	DSC, FTIR, ^{1}H-NMR	Confirms genuine phytoconstituent–excipient interaction (e.g., phytosome complexation) (Gaikwad *et al*., 2021; Semalty *et al*., 2010)
Entrapment/Encapsulation Efficiency	Ultracentrifugation/dialysis followed by HPLC/UV assay	Quantifies the proportion of active successfully incorporated into the carrier (Indrayanto, 2022)
Drug Content and Loading	HPLC/UV assay of the marker or extract per unit of formulation	Confirms label claim and dose uniformity of the formulation (Indrayanto, 2022)
In vitro Release	Dialysis bag/Franz diffusion cell studies	Characterizes release kinetics and predicts in vivo performance (Indrayanto, 2022)
Product-Specific Attributes	pH, viscosity, osmolality; sterility and bacterial endotoxin testing for ocular/parenteral products	Confirms suitability for the intended route of administration
Stability	ICH-aligned accelerated/long-term storage studies	Establishes shelf-life and storage condition requirements (International Council for Harmonisation, 2003)

Table 6: Representative Regulatory and Quality-Control Instruments relevant to Herbal Nanoformulations

Regulatory/Quality Instrument	**Issuing Body**	**Core Requirement Relevant to Herbal Nanoformulations**
WHO Quality Control Methods for Herbal Materials	World Health Organization	Macro/microscopic authentication, chromatographic fingerprinting, marker quantification, GACP/GMP compliance. Citation: (World Health Organization, 2011). Full title: *Quality Control Methods for Herbal Materials*; issued 2011 (updated edition of *Quality Control Methods for Medicinal Plant Materials*, 1998); identifier: ISBN 978-92-4-150073-9; jurisdiction: global (non-binding technical guidance adopted by WHO Member States); applicability: authentication and chemical fingerprinting of herbal raw materials and finished products, including nanoformulated ones; status: current.

Indian Pharmacopoeia (herbal monographs)	Indian Pharmacopoeia Commission	HPTLC/HPLC identity and purity limits for classical herbs (e.g., turmeric, ashwagandha, giloy). Citation: (Indian Pharmacopoeia Commission, 2022). Full title: *Indian Pharmacopoeia 2022*, herbal monographs; issuing authority: Indian Pharmacopoeia Commission, Ghaziabad; identifier: Indian Pharmacopoeia (IP) 2022 (print/online edition); jurisdiction: India (legally binding pharmacopoeial standard); applicability: HPTLC/HPLC identity and purity limits for classical herbs; status: current edition.
AYUSH Pharmacovigilance Programme (Pharmacovigilance Programme for ASU&H Drugs, PvPI-ASU&H)	Ministry of AYUSH, Government of India	Adverse-event and product-quality-complaint reporting for ASU&H formulations. Citation: (Dias & Joshi, 2024; Ministry of AYUSH, 2018). Full title: *Pharmacovigilance Guidelines for ASU&H Drugs (PvPI-ASU&H)*; issuing authority: Ministry of AYUSH, Government of India; year: 2018 (programme ongoing); identifier: Ministry of AYUSH policy guideline; jurisdiction: India; applicability: adverse-event and quality-complaint reporting for Ayurveda, Siddha, Unani and Homoeopathy products; status: current, actively administered.
ICH Q1A(R2)-Aligned Stability Guidance	International Council for Harmonisation	Forced-degradation, accelerated/long-term stability design applicable to nanocarrier-based phytoformulations. Citation: (International Council for Harmonisation, 2003). Full title: *ICH Harmonised Guideline Q1A(R2): Stability Testing of New Drug Substances and Products*; issuing authority: International Council for Harmonisation; year: 2003; identifier: ICH Q1A(R2); jurisdiction: ICH member regions (US, EU, Japan and observer regions); applicability: extended by implication, not by explicit scope, to nanocarrier-based phytoformulations; status: current.
Nanomaterial-Containing Drug Product Guidance	US FDA	Physicochemical characterization (size, PDI, zeta potential) and risk-based evaluation of nanomaterial-containing products. Citation: (US Food and Drug Administration, 2022). Full title: *Drug Products, Including Biological Products, that Contain Nanomaterials—Guidance for Industry*; issuing authority: US Food and Drug Administration; year: 2022 (final guidance, April 2022; first issued as draft guidance in December 2017); identifier: Docket No. FDA-2017-D-0759 (same docket for the draft and final versions); jurisdiction: United States; applicability: physicochemical characterization and risk-based evaluation of nanomaterial-containing drug products, non-binding recommendation; status: current.
Reflection Paper on Nanotechnology-based Medicinal Products	European Medicines Agency	Batch consistency, quality-attribute justification and nanotoxicological risk assessment expectations. Citation: (European Medicines Agency, 2006). Full title: *Reflection Paper on Nanotechnology-based Medicinal Products for Human Use*; issuing authority: European Medicines Agency; year: 2006 (EMEA/CHMP/79769/2006); jurisdiction: European Union; applicability: batch consistency, quality-attribute justification and nanotoxicological risk assessment; status: current reflection paper (non-binding).

Table 7: Representative Patented Technology Platforms and Clinically Evaluated Herbal Nanoformulations

Technology/Product Class	**Phytoconstituent(s)**	**Translational Status/Evidence Type**	**Reference**
Phytosome (phospholipid complex) platform	Silymarin, ginkgo flavonoids, curcuminoids	Foundational patent technology; multiple standardized extract complexes in commercial use	(Bombardelli, 1991)
Phospholipid-complexed curcuminoid formulations	Curcuminoids	Human comparative absorption studies vs. unformulated curcuminoid mixtures	(Cuomo *et al.*, 2011)
Quality-by-Design liposomal co-delivery system	Curcumin (co-encapsulated)	Preclinical long-circulating liposome optimized using design of experiments	(Tefas *et al.*, 2017)
Antidiabetic phytosome optimized using Box–Behnken design	Standardized antidiabetic extract	Preclinical formulation optimization study	(Rathee & Kamboj, 2018)
Curcumin PLGA nanoparticle (nanoprecipitation)	Curcumin	Preclinical in vivo oral bioavailability data	(Shaikh *et al.*, 2009)
3D-printed botanical wound patch	Olive leaf extract	Preclinical in vitro biological property evaluation	(Patitucci *et al.*, 2024)

4. Conclusion

Herbal drug technology has advanced to the point where it is now a science that uses nanotechnology to solve problems of poor solubility, stability, and permeability. These problems have long limited the performance of phytoconstituent-based drugs. Several types of carriers have their own benefits for specific phytoconstituents and routes of delivery. These are vesicles such as phytosomes, liposomes, niosomes, transferosomes, and ethosomes; lipid nanoparticles; self-nanoemulsifying drug delivery systems; polymeric and metal nanoparticles made using green chemistry techniques; and polymers with pores or fibrous structures.

Lasting translational success will need equal effort upstream and downstream. Upstream, it needs rigorous green extraction and standardization by chromatography and/or biomarkers. Downstream, it needs harmonized regulatory and pharmacovigilance policies that take nanomedicine into account, together with active nanotoxicological risk evaluation. Robust quality control links the two. It requires defined limits for the extract and defined and reproducible particle size, zeta potential, entrapment efficiency, release, and stability for the final nanoformulation. The growing convergence of network pharmacology and machine learning offers a promising way to rationalize component selection and formulation design. Experimental verification of such predictions will remain mandatory and not optional. Phytosomes are the only nanotechnology described in this review with decades of human pharmacokinetic data. This illustrates the mature clinical translation of this platform. It also indicates how much time may be needed before the other technologies described in this review reach clinical maturity.

Abbreviations

ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity); **AFM** (Atomic Force Microscopy); **AI** (Artificial Intelligence); **ASU&H** (Ayurveda, Siddha, Unani, and Homoeopathy); **AUC** (Area Under the Plasma Concentration–Time Curve); **AYUSH** (Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homoeopathy, Ministry of AYUSH, Government of India); **BBB** (Blood–Brain Barrier); **Cmax** (Maximum Peak Plasma Concentration); **CNS** (Central Nervous System); **DLS** (Dynamic Light Scattering); **DNA** (Deoxyribonucleic Acid); **DSC** (Differential Scanning Calorimetry); **EMA** (European Medicines Agency); **FDA** (United States Food and Drug Administration); **FTIR** (Fourier-Transform Infrared Spectroscopy); **GACP** (Good Agricultural and Collection Practice); **GC–MS** (Gas Chromatography–Mass Spectrometry); **GI** (Gastrointestinal); **GMP** (Good Manufacturing Practice); **HDT** (Herbal Drug Technology); **HPLC** (High-Performance Liquid Chromatography); **HPLC–DAD** (High-Performance Liquid Chromatography with Diode Array Detection); **HPTLC** (High-Performance Thin-Layer Chromatography); **ICH** (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use); **ICP-MS** (Inductively Coupled Plasma–Mass Spectrometry); **IP** (Indian Pharmacopoeia); **IPC** (Indian Pharmacopoeia Commission); **LC–MS/MS** (Liquid Chromatography–Tandem Mass Spectrometry); **MeSH** (Medical Subject Headings); **NLC** (Nanostructured Lipid Carrier); **NMR** (Nuclear Magnetic Resonance); **PDI** (Polydispersity Index); **PEG** (Polyethylene Glycol); **PK** (Pharmacokinetics); **PLGA** (Poly(lactic-co-glycolic acid)); **PLS–DA** (Partial Least Squares Discriminant Analysis); **PRISMA** (Preferred Reporting Items for Systematic Reviews and Meta-Analyses); **PvPI-ASU&H** (Pharmacovigilance Programme for Ayurveda, Siddha, Unani and Homoeopathy Drugs); **QbD** (Quality by Design); **RH** (Relative Humidity); **SEM** (Scanning Electron Microscopy); **SFE** (Supercritical Fluid Extraction); **SIMCA** (Soft Independent Modelling of Class Analogy); **SLN** (Solid Lipid Nanoparticle); **SNEDDS** (Self-Nanoemulsifying Drug Delivery System); **TCMSP** (Traditional Chinese Medicine Systems Pharmacology Database); **TEM** (Transmission Electron Microscopy); **TPGS** (D-α-Tocopheryl Polyethylene Glycol Succinate); **WHO** (World Health Organization); **XRD** (X-ray Diffraction).

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Ravikant Gupta: Conceptualization, Supervision, Validation, Critical Review, Writing – Review & Editing, Project Administration.

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The authors declare that there are no competing interests associated with this manuscript.

Declarations

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Data sharing is not applicable to this article because no new datasets were generated or analyzed. The information discussed in this review is derived from previously published literature and publicly available sources cited within the manuscript.

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During the preparation and revision of this manuscript, the authors used OpenAI ChatGPT to assist with brainstorming, language editing, and the writing and revision of certain sections. Following the use of this tool, the authors critically reviewed and edited the content as necessary. The authors accept responsibility for the final accuracy, originality, interpretation, and content of the article.

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