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Comparative Evaluation of Phytosomes and Other Vesicular Drug Delivery Systems in Phytopharmaceutical Development

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ABSTRACT:

The clinical translation of phytoconstituents is often restricted by factors like poor aqueous solubility, limited membrane permeability and extensive first-pass metabolism. Vesicular drug delivery systems – including liposomes, niosomes, transferosomes and phytosomes- have emerged as promising carriers in overcoming these pharmacokinetic limitations. Among these, phytosomes, due to its structurally distinct nature, offer improved molecular complexation of phytoactives with phospholipids, ensuring enhanced membrane interaction, systemic absorption and bioavailability. This review provides a systematic comparative analysis of major vesicular systems, highlighting their structural functionalities, physicochemical and biopharmaceutical attributes, safety, toxicity and regulatory perspectives in addition to their application-oriented comparison. This review further analyses the key challenges, research gaps and future perspectives of phytosomal delivery systems and urges the need for standardised characterisation protocols, harmonised regulatory frameworks and validated clinical trials for ensuring their smooth clinical translation. This analysis positions phytosomes as strategically adaptable delivery systems rather than mere bioavailability enhancers, by emphasizing on its integration with formulation science, clinical research and translational validation.

Keywords: Phytosomes, vesicular drug delivery, liposomes, phytopharmaceuticals, bioavailability, phospholipid complexes

INTRODUCTION:

Herbal bioactives and phytoconstituents play a significant role in modern medicinal practices by either complementing synthetic drugs or by exerting improved therapeutic outcomes resulting in preventive healthcare, chronic-disease management and reversing diseased states. They widely contribute to global healthcare through evidence-based applications, especially in areas like metabolic health, immune disorders, cancer therapy, cardiovascular health, women wellness and various other lifestyle conditions. Phytoconstituents like polyphenols, flavonoids, alkaloids, terpenoids and glycosides offer extensive therapeutic applications(1), due to their molecular versatility, pleiotropic actions and favourable risk-benefit ratios; but their use in clinical practice is often limited by challenges associated with their effective delivery and lower bioavailability. Advanced drug delivery systems like vesicular drug delivery system offers promising tools to overcome these limitations of herbal drugs, resulting in targeted and improved therapeutic action.

The therapeutic effectiveness of herbal bioactives is often limited by their physicochemical and biopharmaceutical constraints, including poor aqueous solubility, high molecular size, high crystallinity, complex chemical structure, extensive first-pass metabolism, chemical instability and susceptibility to gastrointestinal degradation leading to reduced systemic bioavailability(2). Curcumin, one of the most extensively investigated phytoconstituents, exhibits low oral bioavailability in clinical studies despite decades of research studies. In addition to oral routes, topical and transdermal delivery of phytoconstituents is equally challenging. These challenges necessitate the need for administering high doses of herbal bioactives, which ultimately compromises patient compliance and risk of increased side-effects.

Vesicular drug delivery systems act as effective delivery systems for delivering synthetic and natural therapeutic agents. Pioneered by Bangham and colleagues in the 1960s with the discovery of liposomes, vesicular delivery systems have evolved tremendously over the last several decades. They typically consist of lipid or surfactant bilayers encapsulating hydrophilic, lipophilic or amphiphilic drug molecules. Some of the most commonly investigated vesicular drug delivery systems include: liposomes, niosomes, phytosomes, transferosomes, ethosomes and other variants like bilosomes (bile-salt enhanced for oral delivery), cubosomes (cubic lipid phases for sustained release) etc. They act as colloidal carriers forming bilayered or multilayered structures, capable of encapsulating or associating with active moieties, resulting in enhances drug solubilization, protection from degradation, controlled or sustained drug release and enhanced cell permeability.

Despite the emergence of competitive vesicular drug delivery systems in phytopharmaceutical research, there is a lack of systematic comparative evaluation of vesicular drug delivery systems, which is grounded on shared evaluation criteria which acts as determinants in selection of suitable vesicular system. The current review focusses on providing a comprehensive, structured and comparative evaluation of phytosomes versus other major vesicular drug delivery systems in identifying critical research gaps and future research potential and limitations of next-generation vesicular systems.

CLASSIFICATION OF VESICULAR DRUG DELIVERY SYSTEMS:

Vesicular drug delivery systems are broadly classified based on their composition, structure, physico-chemical characteristics, drug release kinetics, routes of administration, stability and their applications (3,4) . Table 1 summarises the principal vesicular systems with their core materials, preferred routes of administration and representative products.

Table 1: Classification of major vesicular drug delivery systems with representative examples

System	Core Material	Route of Administration	Representative Products
Phytosomes (3,4)	Phospholipid–phytoconstituent complex (e.g., phosphatidylcholine bound to herbal actives)	Oral; topical	Meriva® (curcumin), Siliphos® (silybin), Greenselect® (green tea)
Liposomes(5,6)	Phospholipids (e.g., phosphatidylcholine) ± cholesterol forming bilayer vesicles	Oral, parenteral, topical, intranasal	*Doxil* (PEGylated liposomal doxorubicin)
Niosomes (7,8)	Non-ionic surfactant bilayers (e.g., Span, Tween) ± cholesterol	Oral, topical, parenteral	Niosomal drug delivery systems for various APIs (in research)
Transfersomes (9,10)	Phospholipids + edge activators (surfactants for elasticity)	Transdermal, topical, mucosal	Elastic vesicle systems for enhanced skin penetration

			(e.g., sertraline, curcumin)
Ethosomes (11)	Phospholipids + high ethanol + water	Topical / transdermal	Epilepsy, skin disorders
Emulsomes(12)	Internal solid lipid core (fat) surrounded by phospholipid bilayer	Oral, topical	Emulsome platforms in research for controlled release
Vesosomes (13,14)	Multivesicular bilayer structures (liposome-derived)	Variable (experimental)	Multilamellar liposomal derivatives
Aquasomes (15)	Ceramic/polymeric core + oligomeric film + drug layer	Experimental	In peptide and protein delivery
Cubosomes (16)	Monoolein/poloxamer cubic lattice	Dermal	Research platforms
Archaesomes (17)	Archaeal ether lipids	Oral, vaccine adjuvants	Immunology research

Phospholipid-based vesicular systems: Phospholipid-based vesicles are primarily composed of endogenous or synthetic phospholipids especially phosphatidyl choline (PC), which undergo spontaneous self-assembly onto bilayered structures in aqueous media (18). Their structural similarity and biocompatibility cell-membranes, make them highly suitable candidates for vesicular drug delivery. Some of the most extensively studies phospholipid-based vesicular systems include liposomes, phytosomes and emulsomes. Liposomes (19) are spherical vesicles with one or more phospholipid bilayers, enclosing an aqueous core. They structurally mimic biologic membranes and is capable of encapsulating either hydrophilic drugs in the aqueous core or lipophilic drugs within the lipid bilayers. They enhance solubility and protects labile phytoconstituents from degradation, but is often associated with limitations like drug leakage and low stability. Nanoliposomes are nanoscale liposomes, with size less than 200nm in diameter, and offering advantages like enhanced cellular uptake, enhanced permeability and increased surface area, but is associated with stability challenges (20). Phytosomes are vesicular systems , whereby phytoconstituents forms molecular complexes with a phospholipid

forming stable complexes, with improved membrane affinity, enhanced oral bioavailability, reduced drug leakage and enhanced stability. These systems are particularly suitable for flavonoids and phenolic compounds possessing polar functional groups, that forms hydrogen bonds (21). Emulsomes consists of a solid or semi-solid lipid core, which is surrounded by a phospholipid bilayer offering high loading efficacy for lipophilic phytoconstituents, while maintaining vesicular characteristics (22).

Surfactant-based vesicular systems: Surfactant-based vesicles are amphiphilic molecules, which form microscopic spherical structures by the self-assembly of non-ionic surfactant molecules in an aqueous environment. Some of the widely studied surfactant-based vesicles include niosomes, proniosomes, transferosomes and ethosomes. Niosomes are one of the most widely used drug delivery systems in topical drug delivery and are made from non-ionic surfactants like Spans or Tweens and are stabilised with cholesterol. They offers high oxidative stability than phospholipid-based systems, with added advantages like lower cost and good entrapment efficiency (23). But they are also associated with disadvantages like lower membrane affinity for certain phytoconstituents and drug leakage due to drug incorporation rather than complexation. Proniosomes are dry, free-flowing formulations that convert into niosomes upon hydration and is more stable during storage (24).

Deformable and modified vesicles: These systems offers enhances permeation, particularly across biological barriers like skin or mucosa. Transferosomes are ultra-deformable vesicles made with surfactants and is used for enhanced transdermal delivery (25). Ethosomes contain high concentrations of ethanol, in addition to phospholipids and water. They disrupt stratus corneum lipids, enhancing skin permeation and offering superior transdermal permeation, but are prone to irritation and stability issues(26).

Novel and hybrid vesicular platforms: Some of the emerging vesicular platforms include phytovesicles, surface-modified vesicles and ligand-targeted systems, which offers improved targeting, stability and therapeutic precision. Phytovesicles have multi-component herbal extracts with improved phospholipid complexation techniques and are designed for enhances stability and multi-target therapy (27). Surface modification of vesicles with polymers like PEG (28) or bio-adhesive materials results in vesicular systems with prolonged circulation time, reduced opsonization and improved mucosal adhesion. Targeting the vesicles with ligands like antibodies, peptides, folates and aptamers (29) offers site-specific delivery, reduced systemic toxicity and enhanced therapeutic precision.

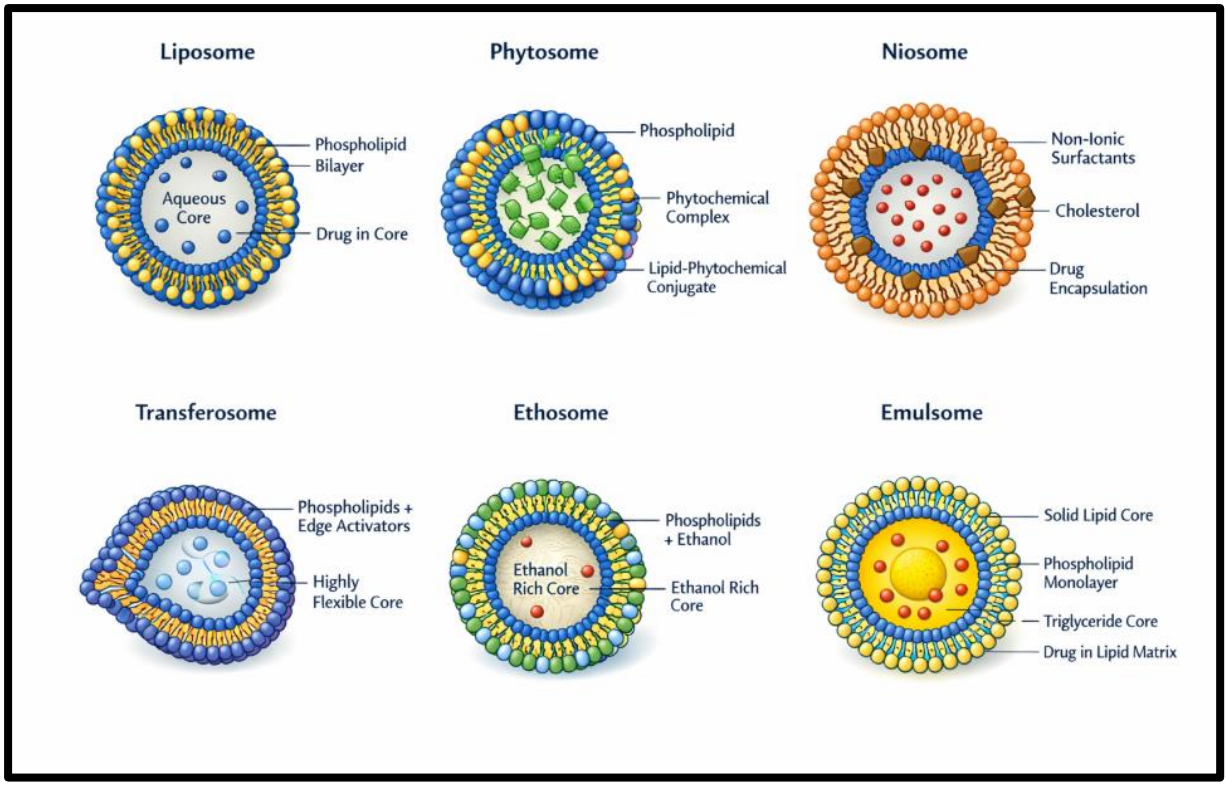

Figure 1: Schematic representation of the structural organization and compositional differences among liposome, phytosome, niosome, transfersome, ethosome, and emulsome.

CRITERIA FOR COMPARATIVE EVALUATION OF VESICULAR DRUG DELIVERY SYSTEMS:

A rigorous comparative evaluation of vesicular drug delivery systems requires a multi-dimensional assessment including intrinsic formulation properties and extrinsic performance parameters involving but not limited to drug incorporation strategy, physicochemical behaviour, biological performance and translational feasibility. The following criteria are adopted in this review for ensuring a systematic and scientifically justifiable assessment.

Drug incorporation mechanism: The mechanism of phytoconstituent association with the vesicular system is one of the primary determinants of stability, loading efficiency and release behaviour. Physical entrapment of the active within the aqueous core (hydrophilic moiety) or within the lipid bilayer (lipophilic moiety) is one of the most commonly seen drug incorporation mechanisms. Vesicular systems like liposomes, niosomes, transferosomes and ethosomes commonly exhibit this mechanism (30,31). However, they are associated with drawbacks like drug leakage over time, burst release phenomena and limited membrane integration. Molecular complexation is another major drug incorporation mechanism seen in

vesicular systems, wherein the phytoconstituent forms a stoichiometric complex with phospholipids via hydrogen bonding or polar interactions (32). Phytosomes commonly exhibit this type of drug incorporation and therefore offer advantages like low leakage, enhanced membrane affinity, improved oral absorption and greater chemical stability.

Physico-chemical characteristics: The key physico-chemical parameters influencing the in vivo performance, targeting capability and reproducibility of vesicular systems include particle size, polydispersity index, zeta potential and morphology (33–35). These parameters together influence how vesicles behave in gastrointestinal fluid, blood circulation and dermal layers. Particle size determines cellular uptake and biodistribution behaviour of vesicles, wherein particle size <200nm is preferred for enhanced absorption. A low poly dispersity index (<0.3) indicates particle size uniformity and greatly impacts reproducibility and scalability. Zeta potential indicates surface charge and colloidal stability and a value of ±30 mV is generally considered to have good stability. The morphology of vesicles critically influences the targeting and stability of phytoactives.

Stability and shelf-life: The thermodynamic and kinetic stability of vesicular systems under relevant storage and physiological conditions is a critical determinant of their clinical utility. Physical stability concerns like particle aggregation, flocculation, sedimentation and chemical instability indicators like oxidation of phospholipids, hydrolysis of ester bonds and degradation of phytoconstituents greatly influences shelf life of the vesicles. Entrapment-based vesicles are prone to drug leakage over time.

Biopharmaceutical performance: The biopharmaceutical performance evaluation of vesicles involves a critical analysis of in vitro release behaviour, membrane permeation enhancement and in vivo pharmacokinetic behaviour, including absolute bioavailability, peak plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), area-under the plasma-concentration time curve (AUC) and elimination half-life.

Safety and regulatory acceptability: Safety evaluation of vesicular system encompasses acute and chronic toxicity concerns involving safety of excipients, residual solvents and manufacturing process-related impurities in addition to its biocompatibility, immunogenicity and genotoxic potential.

Industrial scalability and Cost: Industrial translation of these vesicular systems often depends on raw material availability, manufacturing complexity, batch-to-batch reproducibility and commercial viability.

PHYTOSOMES AS A BENCHMARK VESICULAR SYSTEM:

Phytosomes represent a structurally distinct and mechanistically unique platform for herbal drug delivery, due to their biopharmaceutical advantages. Unlike conventional vesicles, wherein the drug is entrapped within the vesicles, phytosomes involve molecular complexation of phytoconstituents with the phospholipids, ensuring superior drug delivery and stability.

Phytosomes are lipid-compatible molecular complexes, formed by phytoconstituents like polyphenols, flavonoids or phenolic acids and phospholipids, wherein they form stable complexes through hydrogen bonding of the polar heads of phospholipids and active (36). Most of the phytoconstituents contain either hydroxyl groups, carboxyl groups or carbonyl groups as their functional groups and form stable complexes with the phosphate or ammonium group of phosphatidylcholine, through hydrogen bonding, polar electrostatic interaction or van der Waals stabilisation. Upon complexation, these drug-phospholipid conjugates self-assemble into micelles or vesicular structures exhibiting amphiphilic behaviour. The commonly used preparation methods for phytosomes are the solvent evaporation method, anti-solvent precipitation method and thin-film hydration method. Phytosomes offer unique biopharmaceutical advantages justifying their benchmark status. They offer advantages like enhanced membrane permeability, improved oral bioavailability, improved chemical stability, reduced drug leakage and improved pharmacodynamic efficiency. However, they are associated with limitations like their limited suitability for highly hydrophilic macromolecules, risk of phospholipid oxidation, cost feasibility and minimal transdermal applications (37–39).

COMPARATIVE ANALYSIS: PHYTOSOMES VERSUS OTHER VESICULAR SYSTEMS:

The following comparative analysis evaluates phytosomes against other major vesicular drug delivery systems in terms of structural organisation, drug-carrier interaction, stability, pharmacokinetics and translational feasibility.

Table 2: Comparative Evaluation of Phytosomes and Other Vesicular Drug Delivery Systems

Comparative Parameter	Phytosome	Liposome	Niosome	Transfersome	Ethosome	Emulsome

Core Structural Concept	Drug–phospholipid molecular complex	Phospholipid bilayer vesicle	Nonionic surfactant bilayer vesicle	Ultra-deformable phospholipid vesicle with edge activator	Ethanol-rich phospholipid vesicle	Solid lipid core surrounded by phospholipid shell
Drug Incorporation Mechanism	Molecular complexation (hydrogen bonding & polar interactions)	Physical entrapment	Physical entrapment	Physical entrapment	Physical entrapment	Drug solubilized in solid lipid core
Drug Location	Drug becomes part of membrane architecture	Hydrophilic → aqueous core; Lipophilic → bilayer	Similar to liposomes	Similar to liposomes	Similar to liposomes	Mainly lipophilic drug in solid core
Interaction Strength	Strong association (quasi-chemical complex)	Weak, reversible	Weak, reversible	Weak, reversible	Weak, reversible	Physical solubilization
Risk of Drug Leakage	Low	Moderate to high	Moderate	Moderate	Moderate	Low for lipophilic drugs
Oxidative Stability	Moderate (phospholipid oxidation possible)	Moderate (susceptible to oxidation)	Higher (less prone to oxidation)	Moderate	Moderate	Higher (solid lipid stabilizes)

Moisture Sensitivity	Moderate	Moderate	Lower	Moderate	Moderate	Low–moderate
Membrane Deformability	Moderate	Moderate	Moderate	Very high (ultra-deformable)	High (ethanol fluidizes membrane)	Low
Mechanism of Absorption Enhancement	Lipid compatibility + improved membrane permeation	Protection + solubilization	Protection + solubilization	Deformability through skin pores	Ethanol-mediated membrane disruption	Sustained release + lymphatic uptake
Oral Bioavailability Enhancement	High (especially for polyphenols)	Moderate	Moderate	Limited (not designed for oral use)	Limited (not for oral use)	High for lipophilic drugs
GI Stability	Improved due to complexation	Limited (bile salt disruption possible)	Moderate	Not primary use	Not primary use	Good for lipophilic drugs
Lymphatic Transport Potential	Significant	Limited to moderate	Limited	Minimal	Minimal	High
Suitability for Polar Phytoconstituents	Excellent (ideal for flavonoids, phenolics)	Moderate	Moderate	Limited	Limited	Poor
Suitability for Lipophilic Phytoconstituents	Moderate	Good	Good	Moderate	Moderate	Excellent

Best Route of Administration	Oral systemic delivery	Oral, parenteral, topical	Oral, topical	Transdermal	Dermal/transdermal	Oral (lipophilic drugs)
Performance in Transdermal Delivery	Moderate	Moderate	Moderate	Superior	Superior	Limited
First-Pass Metabolism Reduction	Yes (lymphatic uptake)	Limited	Limited	Yes (via transdermal route)	Yes (via transdermal route)	Yes
Excipient Biocompatibility	High (phosphatidylcholine-based)	High	Moderate (depends on surfactant)	High	Ethanol-related concerns	High
Irritation Potential	Low (oral)	Low	Moderate (surfactant dependent)	Low	Possible (ethanol irritation)	Low
Regulatory Acceptance	Good (commercial phytosome products exist)	Strong (established system)	Moderate	Moderate	Moderate (ethanol scrutiny)	Emerging
Commercial Translation	Strong nutraceutical presence	Widely commercialized (pharma)	Limited	Mostly research-stage	Mostly research-stage	Limited

Industrial Scalability	Moderate (requires stoichiometric precision)	Established but complex	Easier and cost-effective	Complex	Moderate	Moderate
Raw Material Cost	Higher (purified phospholipids)	Higher	Lower	Higher	Higher	Moderate
Clinical Evidence for Herbal Extracts	Strong (e.g., flavonoid phytosomes)	Moderate	Limited	Limited	Limited	Limited
Major Limitation	Limited drug loading (stoichiometric ratio)	Leakage & instability	Surfactant toxicity concerns	Not suited for oral systemic therapy	Ethanol volatility & irritation	Mainly for lipophilic drugs

Physicochemical attributes involving particle size distribution, surface charge, morphology, drug loading capacity, release kinetics and storage stability are critical determinants of the invivo behaviour, therapeutic performance and clinical translatability of vesicular drug delivery systems .

Table 3: Comparative physicochemical attributes of major vesicular drug delivery systems

Parameter	Phytosome	Liposome	Niosome	Transferosome	Ethosome	Emulsome
Particle Size (nm)	100–800	50–300	100–1000	100–300	150–800	200–600
Zeta Potential (mV)	−30 to −50	−20 to −40	−30 to −50	−25 to −45	−20 to −40	−30 to −50
Encapsulation Eff. (%)	70–95	30–80	50–90	60–85	60–90	50–85
Drug Incorporation	Complexation	Bilayer entrap.	Bilayer entrap.	Bilayer entrap.	Bilayer entrap.	Core partition
Bilayer Stability	High	Moderate	Moderate	Low–Moderate	Moderate	High
Drug Leakage	Minimal	Significant	Moderate	High	Moderate	Low
Shelf-life (months)	18–24	6–12	12–18	6–9	6–12	12–18

The safety profile of vesicular drug delivery involves assessment of the inherent toxicity of carrier excipients, manufacturing process-related impurities, potential for immunogenicity and regulatory acceptability.

Table 4: Comparative safety and regulatory profile of major vesicular drug delivery systems

Parameter	Phytosome	Liposome	Niosome	Transferosome	Ethosome	Emulsome
Key Excipients	PC, solvent	PC, cholesterol	Span, Tween	PC, edge activator	PC, ethanol	PC, lipid
GRAS Status	Yes (PC)	Yes	Partial (Span)	Yes	Partial (ethanol)	Yes
Toxicity Risk	Low	Low–Moderate	Low	Low	Moderate (ethanol)	Low
Immunogenicity	Low	Moderate (PEGylated low)	Low	Low	Low	Low
Regulatory Precedent	Nutraceutical	Pharmaceutical (IV)	Cosmetics	Cosmetics	Cosmetics	Pharma (IV)
Clinical Trial Data	Moderate (nutra)	Extensive	Limited	Limited	Limited	Limited

Eventhough, physicochemical parameters and safety profiles provides an insight towards the suitability of various vesicular systems, the true differentiation of vesicular drug delivery systems emerges with its therapeutic contexts which involves the intended route of administration, disease chronicity and required pharmacokinetic profile of the phytoactive. This section particularly focuses on metabolic syndrome and related chronic inflammatory disorders because they need long-term administration, involving multi-target phytoconstituents and often demand sustained systemic exposure with minimal toxicity. Phytosomes offer superior oral bioavailability through improved aqueous dispersibility, phospholipid-facilitated

membrane permeation, partial protection from gastrointestinal degradation, reduction of first-pass metabolism and potential lymphatic absorption. Preclinical comparisons show superior AUC-to-dose relationships of curcumin phytosomes compared to their liposomal, nanoparticle or conventional extract formulations in oral pharmacokinetic studies, reinforcing the translational advantage of phytosomal complexes for polyphenolic actives (40–44).

Metabolic disorders like type 2 diabetes mellitus, non-alcoholic fatty liver disease, dyslipidaemia, obesity-associated inflammation and cardiovascular syndromes shares same pathophysiological features, including low-grade systemic inflammation, oxidative stress, insulin resistance, adipose tissue dysfunction and hepatic steatosis. Polyphenols like curcumin, quercitin, resveratrol, berberine and green tea catechins exhibit pleiotropic pharmacological effects addressing these mechanisms, but suffer from limitations like low oral bioavailability affecting their clinical utility. Phytosomes particularly align with long-term therapy of chronic disorders by prioritising long-term safety, oral convenience, patient compliance, cost-effectiveness and good stability. Silybin administration in non-alcoholic steatohepatitic conditions as phytosomes demonstrates significantly demonstrates greater AUC compared to silymarin extract, with documented evidence of increased hepatoprotective activity and compliance (45–48).

CHALLENGES, RESEARCH GAPS AND FUTURE PERSPECTIVES:

Eventhough vesicular drug delivery systems- particularly phytosomes offers significant therapeutic advantages, their scientific, methodological and translational challenges remain. Despite their biopharmaceutical and therapeutic advancements, key challenges like structural and formulation complexity, phospholipid stability issues, scale-up and manufacturing constraints, cost-considerations and regulatory classification ambiguity limits their utility in clinical settings. Addressing these gaps is essential for advancing phytosomal technology from

nutraceutical optimization to evidence-based pharmaceutical integration. Absence of well-designed, controlled comparative studies evaluating phytosomes against liposomes, niosomes, transferosomes and polymeric nanoparticles under identical experimental conditions results in lack of a head-to-head comparison of vesicular delivery systems. In addition several studies based on phytosomal formulations shows a lack of standardised characterization and evaluation criteria. There is a need to address the existing research gaps through standard evaluation protocols, mechanistic absorption studies, multicentre clinical trials and harmonized regulatory frameworks.

Future phytosomal formulation must shift from trial-and-error formulation to mechanistic optimization-based formulations by integrating approaches like molecular docking, molecular dynamic simulation and physiologically based pharmacokinetic modelling (PBPK) enabling predictive formulation designs rather than empirical iterations. Targeted and functionalized phytosomes based on next-generation approaches like ligand-modified phospholipids, mannosylated systems, folate-conjugated systems and PEGylated phytosomes must be engineered to enhance tissue selectivity, therapeutic index and dose reduction. Bioinspired phytosomes incorporating phospholipids derived from marine sources (phosphatidylserine, ether phospholipids from krill oil) offer unique immunomodulatory and neuroprotective properties beyond carrier function. Complexation of phytosomes with solid lipid matrices is being studied for its enhanced physical stability and offers promising initial results. Quantum computational chemistry approaches applied to phytosome complexation dynamics could provide atomistic insights into the binding energy landscape of phytoconstituent-phospholipid interactions, guiding rational design of next-generation complexes.

CONCLUSION:

Vesicular drug delivery plays significant role in leveraging the therapeutic potential of plant-derived bioactives, particularly those limited by factors like poor aqueous solubility, low

membrane permeability and extensive first-pass metabolism. Among these systems, phytosomes play a distinct role in improving the absorption efficiency, systemic exposure and clinical performance of phytoactives, especially polyphenolic compounds due to its structurally distinct nature. Comparative evaluations emphasize that phytosomes are particularly suited for oral delivery of lipophilic polyphenols especially in diseases of chronic nature like metabolic and inflammatory disorders characterized by oxidative stress, low-grade systemic inflammation, insulin resistance, and tissue dysfunction.

However, constraints like limited head-to-head comparative trials, inconsistent characterization standards, regulatory ambiguity and long-term clinical studies needs to be addressed through standardized evaluation protocols, mechanistic absorption studies, multicentre clinical trials and harmonized regulatory frameworks. Future progress through targeted and functionalized phytosomal delivery, predictive computational modelling and hybrid delivery architectures through formulation innovations and strategic integration of mechanistic science needs to be adopted for clinical evidence generation.

In conclusion, phytosomes should be uniquely positioned to serve both as benchmark vesicular platform and as the architectural foundation upon which next-generation intelligent phytodelivery systems will be constructed.

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