Formulation and Evaluation of Phytosome Drug-Delivery Systems: A Systematic Review

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Abstract

Background: Many plant-derived actives (polyphenols, flavonoids, select terpenoids) show potent in-vitro effects yet suffer poor oral performance due to low solubility, weak membrane permeability, instability, and first-pass metabolism. Phytosomes—stoichiometric drug–phosphatidylcholine (PC) complexes—were developed to convert these molecules into amphiphiles with high bilayer affinity, thereby improving delivery without altering intrinsic pharmacology. **Methods:** We conducted a PRISMA-guided synthesis of the phytosome literature, extracting formulation practices (PC grade, drug:PC ratios, solvents/processes), complexation analytics (FTIR/NMR/DSC/XRD), critical quality attributes (CQAs), route-matched performance tests (release, permeability, lipolysis), stability programs, and translational outcomes. We additionally mapped "polymer add-ons" (e.g., chitosan, HA, PEG/DSPE-PEG, poloxamers, cellulose ethers, carbomer, alginate/pectin, enterics, PLGA/PCL, saccharide glass-formers) to practical use cases. **Results:** Across preparation routes (thin-film, anti-solvent precipitation, slurry/reflux, co-grinding; solid conversion by lyophilization/spray-dry), verified complexation correlated with favorable CQAs (typical targets: 80–250 nm, PDI ≤ 0.30, $|\zeta| \geq$ 20–30 mV, EE% ≥ 70%) and with biopharmaceutic gains: co-solubilization with bile, enhanced membrane partitioning, and partial lymphatic transport. Reported exposure increases versus non-complexed forms commonly ranged ~1.4–7-fold. Human data show higher oral exposure for silybin and quercetin; curcumin–PC improved osteoarthritis symptoms with good tolerability; catechin phytosomes aided weight loss/maintenance. Preclinical upgrades were consistent for resveratrol, baicalein/baicalin (including SMEDDS hybrids), ginkgo (brain antioxidant readouts), and topical rutin (skin deposition). Polymers functioned as route-specific enablers—mucoadhesion

(chitosan/TMC), hydration/targeting (HA), steric stabilization (DSPE-PEG), thermogelling/process protection (poloxamers), viscosity/gels (cellulose ethers, carbomer), GI targeting (alginate/pectin, enterics), depots (PLGA/PCL), and powder engineering (dextran/pullulan/maltodextrin). Quality discipline—validated assays per ICH Q2(R2)/Q14 and stability to Q1A(R2)—was decisive for reproducibility. **Limitations:** Evidence is heterogeneous: incomplete disclosure of PC grade/fatty-acid profile and solvent histories, variable complexation proof, inconsistent EE% separations and DLS reporting, few ICH-style stability datasets, and limited, underpowered clinical trials with scarce head-to-head comparators. Safety aspects (e.g., anti-PEG responses, lipid peroxidation, leachables) are inconsistently profiled. **Conclusions:** When genuine drug–PC complexation is achieved and CQAs are controlled, phytosomes provide a generalizable path to improve exposure and, in select indications, clinical outcomes. Progress now hinges on standardized reporting, mechanistic biopharmaceutics (lipolysis–permeation, lymphatic quantification, PBPK), larger head-to-head RCTs, QbD-guided scale-up (including continuous spray-dry or SAS), and polymer innovation with systematic immunocompatibility testing.

Keywords: phytosome; phosphatidylcholine complex; polyphenols; bioavailability; polymer coating; SMEDDS; Quality-by-Design; ICH stability; lymphatic transport; osteoarthritis.

1. Introduction

Many plant-derived bioactive—particularly polyphenols, flavonoids, and select terpenoids—exhibit robust antioxidant, anti-inflammatory, and metabolic activities *in vitro* but translate poorly in humans due to low aqueous solubility, limited membrane permeability, chemical/enzymatic instability, and extensive first-pass metabolism, with many falling into BCS Class II/IV [1,2]. These biopharmaceutic hurdles produce low and variable oral exposure, forcing high nominal doses that complicate adherence and obscure clear dose–response relationships [2]. Phytosomes (phyto-phospholipid complexes) were designed to address these bottlenecks by forming stoichiometric molecular adducts between a phytoconstituent (e.g., phenolic –OH/carbonyl groups) and the polar headgroup of a phospholipid—most commonly phosphatidylcholine (PC) [3–5]. Unlike liposomes, which physically encapsulate solutes within an aqueous core or bilayer, phytosomes depend on specific hydrogen-bonding/ionic and π–π interactions to yield an amphiphilic complex with improved membrane affinity and protection from hydrolysis/oxidation [3–6]. Evidence of true complexation is typically corroborated by spectroscopic (FTIR/NMR;

characteristic band and chemical-shift changes) and thermal (DSC; melting-point depression/new endotherms) signatures, supported by XRD peak attenuation/broadening [4,6,7]. Preparative routes include thin-film hydration/solvent evaporation, slurry/anti-solvent precipitation, and related co-solvent methods, often followed by freeze- or spray-drying to produce solid intermediates suitable for downstream dosage forms [4,5]. Critical input variables—PC grade/purity, drug:PC molar ratio (commonly 1:1–1:3), solvent system, hydration pH/ionic strength, and post-processing—determine critical quality attributes (CQAs) such as particle size/PDI, zeta potential, entrapment efficiency (EE%), drug content, and solid-state form [4,5,8]. Because these CQAs steer dissolution, membrane partitioning, and stability, validated analytical methods (per ICH Q2(R2)/Q14) are essential for credible characterization and batch comparability [12]. From a biopharmaceutic perspective, phytosomes aim to improve transcellular transport and stabilize labile moieties, thereby increasing permeability and oral bioavailability. Typical evaluation spans DLS (size/PDI), electrophoretic light scattering (zeta), ultrafiltration/centrifugation for EE% with recovery checks, FTIR/DSC/XRD/NMR for complexation, *in-vitro* release, PAMPA/Caco-2 permeability, *ex vivo* intestinal models, and translation to *in-vivo* pharmacokinetics (AUC, Cmax) and—where available—clinical outcomes [4,5,8,9]. Long-term stability should follow ICH Q1A(R2) at 25–30 °C (long-term/intermediate) and 40 °C/75% RH (accelerated) using stability-indicating assays [11,12]. Clinical and preclinical proofs-of-concept include the silybin–PC complex, which yielded higher plasma exposure in humans than uncomplexed silymarin/silybin [6], and improved oral PK in rats versus plain silybin [10]. Downstream exemplars—curcumin–PC in osteoarthritis and catechin phytosomes (Greenselect Phytosome®) for weight-management adjunct therapy—suggest that enhanced exposure can translate to symptomatic or metabolic benefits [9,13,14]. Similar trends are reported for other flavonoids (e.g., quercetin, baicalin), with ~1.4–7-fold exposure gains over non-complexed counterparts in preclinical settings [4,7]. Despite rapid adoption, the literature remains heterogeneous: PC grade/fatty-acid profile is often under-reported; drug:PC ratios vary without thermodynamic justification; complexation evidence (FTIR/DSC/XRD/NMR) may be incomplete; EE% methods sometimes lack validated phase separation; DLS settings (dispersant viscosity/RI) are inconsistently disclosed; ICH-aligned stability is variably assessed; and clinical trials beyond early exemplars are few and underpowered [4,5,8,11,15]. These inconsistencies hamper cross-study comparisons and obscure process–structure–performance relationships.

Objective. To address these gaps, we conduct a PRISMA-guided systematic review to (i) catalog formulation practices (materials disclosure and drug: PC stoichiometry), (ii) synthesize CQAs and confirmatory analytics of complexation, (iii) summarize permeability, pharmacokinetics, and stability versus non-complexed comparators, and (iv) identify reporting standards and methodological priorities that could accelerate robust phytosome development and clinical translation [4,15]. Hypothesis statement (concise). We hypothesize that phytosomes form true drug–phospholipid complexes that, when prepared with well-specified inputs/processes (e.g., PC purity ≥ 90%, drug:PC 1:1–1:2, controlled solvent–hydration and solid-state conversion), achieve favorable CQAs (80–250 nm, PDI ≤ 0.30, $|\zeta| \geq 20$–30 mV, EE% ≥ 70%) which mediate superior permeability and dose-normalized exposure versus non-complexed comparators; that polyphenols/flavonoids derive the largest gains; and that ICH-aligned analytical rigor and stability reduce variability and support clinical translation [2,7–12].

2. Phytosome Drug Delivery: Methods, Polymers, and Performance

Phytosomes are drug–phospholipid complexes; polymers are added around them to solve practical problems—preventing aggregation, improving mucosal residence, tuning release, protecting in gastric acid, enabling drying to powders, or targeting specific tissues [22,28,32,33]. The right polymer choice depends on route (oral, nasal, topical, parenteral), processing constraints (aqueous vs organic), and the phytochemical's sensitivity. Below, each polymer (or family) is discussed in prose with typical benefits and trade-offs.

2.1. Chitosan and derivatives (e.g., chitosan HCl, trimethyl chitosan) are the most used cationic coats for phytosomes intended for oral, buccal, and nasal delivery. Their positive charge promotes mucoadhesion and can transiently open tight junctions, increasing epithelial permeation. Coating is straightforward via electrostatic adsorption onto the negatively charged phosphatidylcholine surface, often boosting ζ-potential and colloidal stability in acidic media. The trade-offs are pH-dependent solubility (loss of solubility and flocculation near neutral pH), batch variability in molecular weight/degree of deacetylation, and a risk of charge-related cytotoxicity at higher coating levels; careful titration and buffering are essential [16–18].

2.2. Hyaluronic acid (HA) is a hydrophilic anionic polysaccharide used to give phytosomes a "stealthy" hydration shell and, importantly, to exploit CD44-mediated interactions in inflamed or tumor tissues. HA coatings can reduce opsonization and improve comfort for topical and intra-articular use, and in layer-by-layer builds it's often paired over a chitosan priming layer.

Limitations include enzymatic degradation by hyaluronidases in vivo (which can shorten residence time), potential reduction in epithelial uptake due to negative charge, and cost; molecular-weight selection balances stability with tissue penetration [19].

2.3. Alginate and pectin are classic anionic, gel-forming polysaccharides used to entrap or coat phytosomes for gastro-resistant oral formats. Calcium-crosslinked alginate beads protect in gastric acid and release in the intestine; pectin can bias colonic release via microbiota-driven degradation. These systems are inexpensive and GRAS, but gels may be brittle, susceptible to acid de-gelation if crosslinking is weak, and show variability with alginate M/G ratio or pectin degree of esterification; adding plasticizers or secondary polymers mitigates friability [20,21].

PEGylation (free PEG or, preferably, DSPE-PEG embedded in the phospholipid shell) provides steric stabilization, improved serum compatibility, and better redispersion after freeze-drying. PEG layers reduce protein adsorption and aggregation, which is valuable for parenteral or long-circulating research formats and also helps topical stability. The downside is a potential anti-PEG antibody/accelerated-blood-clearance (ABC) phenomenon on repeat dosing, possible reduction in cellular uptake due to the hydration layer, and increased cost; minimal PEGylation (e.g., 1–5 mol% DSPE-PEG) often balances stability with uptake [22–25,34].

2.4. Poloxamers (Pluronic F68/F127) are non-ionic block copolymers that lower interfacial tension and protect phytosomes during shear, filtration, and lyo. F127 uniquely forms thermoreversible gels, enabling in-situ gelling nasal or topical systems where the dispersion becomes a soft gel at body temperature, extending residence time. Potential drawbacks are micelle formation at higher concentrations that can compete with or extract lipids from the phytosome surface, and pronounced viscosity increases that may slow drug release; concentrations should be optimized to avoid over-micellization [26,27].

2.5. Polyvinylpyrrolidone (PVP; K30/K90) is a versatile hydrogen-bonding stabilizer and lyoprotectant that improves redispersibility after spray- or freeze-drying and can serve as a film former in solid oral intermediates. It helps suppress Ostwald ripening and supports robust powder handling. Being hygroscopic, PVP can raise water uptake and tackiness under humid storage, and—by competing for hydrogen bonding—may slightly reduce entrapment efficiency if used excessively; moisture-barrier packaging and moderate inclusion levels alleviate this [28].

2.6. Cellulose ethers (HPMC, HPC, NaCMC) are used to tune viscosity in liquid dispersions, create mucoadhesive gels, or cast films and matrix tablets containing phytosomes. They are GRAS,

widely available, and excellent for controlling release kinetics and improving topical spreadability. The main disadvantages are potential over-viscosity that slows drug release excessively, slow hydration (a processability issue), and batch-to-batch differences in substitution patterns that can alter gel behavior; selecting pharmacopeial grades and specifying viscosity ranges is key [29].

2.7. Carbomer (Carbopol®) produces high-clarity, pH-responsive gels at very low concentrations and provides strong mucoadhesion—ideal for topical, ocular, or buccal phytosome gels. After neutralization (e.g., with triethanolamine), it offers excellent spreadability and holds particles in a stable network. Pitfalls include sensitivity to the type and amount of neutralizer (over-neutralization or multivalent cations can destabilize phospholipids), potential entrapment that retards release if gel strength is too high, and incompatibility with very low pH or high electrolyte loads; rheology screening prevents over-gelation [30].

2.8. Polyvinyl alcohol (PVA) is favoured for clear, tough films and as a cryoprotectant in freeze-drying. In wound dressings or transdermal-style films, PVA provides mechanical integrity and uniform phytosome distribution. The trade-offs are limited biodegradability, a tendency to form dense matrices that can slow release if plasticization is inadequate, and the need to control residual acetate; using plasticizers (e.g., glycerol) and partial-hydrolysis grades tailors performance [31].

Enteric polymers—Eudragit® (methacrylate copolymers) and HPMCP/HPMCAS—enable pH-triggered protection and site-specific release. Eudragit L/S dissolves above pH ~6.0–7.0 for intestinal delivery; RS/RL grades afford time-controlled diffusion. HPMCP/HPMCAS offer aqueous dispersions with reliable enteric performance. These coats shield phytosomes from gastric acid, but often require organic solvents (for some Eudragit systems), plasticizers to prevent brittle films, and careful curing; incompatibilities with residual solvents or quaternary ammonium groups should be checked to protect the phospholipid complex [29].

2.9. Biodegradable polyesters (PLGA, PCL) are used when a sustained-release or depot effect is desired, embedding phytosomes within microspheres, nanofibers, or implants. This hybrid "phytosome-in-polymer" approach provides mechanical protection and extended release tunable by polymer molecular weight and composition. Disadvantages are the need for organic-solvent processing (with rigorous residual-solvent control), potential acidic microenvironments during PLGA degradation that can destabilize sensitive phytochemicals, and increased manufacturing and regulatory complexity [32].

2.10. Saccharide carriers—dextran, pullulan, maltodextrin, gum arabic—excel as spray- or freeze-dry bulking agents and wall materials for converting phytosome dispersions to free-flowing powders or granules. They improve powder flow and redispersibility and can be food-grade when needed. Their hygroscopicity demands moisture-barrier packaging, and high loadings can increase reconstituted particle size or viscosity; balancing solids content and adding small amounts of surfactant typically restores target CQAs [33].

Table 1. Polymers with phytosomes—role, pros/cons, and typical use levels.

Polymer	Main role with phytosomes	Key advantages	Key disadvantages	Typical use
Chitosan	Mucoadhesive, cationic coat	↑ Residence & permeability; +ζ	pH-limited solubility; aggregation risk; cytotoxicity at high charge	0.05–0.3% w/v coat
Hyaluronic acid	Targeting (CD44), stealth	Biocompatible; ↓ opsonization	Enzymatic degradation; −ζ may reduce uptake	0.05–0.2% w/v
PEG / DSPE-PEG	Steric stabilization	Prolongs circulation; lyo-friendly	ABC/anti-PEG risk; ↓ uptake; cost	1–5 mol% (DSPE-PEG)
Poloxamer F68/F127	Stabilizer / thermogel	Protects during shear/lyo; in-situ gel (F127)	Micelle competition; viscosity ↑	F68 0.05–0.5%; F127 16–22%
PVP (K30/K90)	Stabilizer, lyoprotectant, film	Redispersibility; processable	Hygroscopic; may lower EE% slightly	0.5–3%
HPMC/HPC/Na CMC	Viscosity/film for oral/topical	GRAS; release control	Too viscous → slow release	0.2–1% gel; 2–10% film
Carbomer	Topical gel matrix	Strong mucoadhesion; pH-swelling	Needs neutralizer; may destabilize lipids if mis-formulated	0.1–0.5%
Alginate/Pectin	Beads, gastro-resistance	Simple ionic gelation; colon targeting	Brittle; acid de-gelation	1–2% + Ca^{2+}
Eudragit L/S/RS/RL	Enteric/controlled release	pH-triggered release	Often needs organic solvent; brittle	5–12% solids (coat)
PVA	Film/cryoprotectant	Tough clear films	Limited biodegradation	2–10% film
PLGA/PCL	Sustained-release depot	Strong protection; tunable release	Solvent exposure; acidic microenv.	2–10% in organic phase

Dextran/Pullulan/ Maltodextrin	Spray-/freeze-dry carrier	Redispersibility; food-grade	Hygroscopic; size ↑ on reconst.	10–40% solids (spray-dry)

3. Mechanism of action of Phytosome

Figure 1A — Complexation (making the amphiphile). A phytosome is a stoichiometric complex between a phytoconstituent (often a polyphenol) and the phosphatidylcholine (PC) headgroup. Hydrogen bonding (O–H…O=P; C=O…H–O), ionic contacts (when ionizable groups are present), and π–π stacking with choline-adjacent motifs reorganize the solute's microenvironment. This amphiphilic switch increases membrane affinity and suppresses crystallization; it's not mere encapsulation (as in liposomes) but a molecular adduct. Orthogonal confirmation uses FTIR/NMR (diagnostic shifts), DSC (new/shifted endotherms), and XRD (peak attenuation/broadening). **Figure 1**B — Dissolution & mixed micelles (intestinal phase). Upon oral dosing, the complex disperses and co-solubilizes with bile salts and PC to form mixed micelles in the lumen. These structures raise the apparent solubility of hydrophobic phytochemicals and keep them in a membrane-seeking state adjacent to enterocytes. The higher micellar activity improves the concentration gradient and reduces precipitation when gastric contents transition to the small intestine. **Figure 1**C — Membrane partitioning & lymphatic transport. At the brush border, the amphiphilic complex partitions directly into the apical membrane (transcellular diffusion). A fraction of highly lipophilic complexes can be incorporated into pre-chylomicron particles (MTP-dependent), enter intestinal lymph, and drain via lacteals to the systemic circulation, bypassing part of first-pass metabolism. Together these routes raise dose-normalized AUC/Cmax. **Figure 1**D : Protection from degradation. The PC microenvironment shields labile groups (e.g., phenolic –OH) from hydrolysis/oxidation and limits aqueous aggregation. Reduced crystallinity and tighter molecular packing slow chemical and physical instability, preserving the deliverable fraction during GI transit and storage. **Figure 1**E — Endocytic uptake options. Beyond passive partitioning, nanoscale aggregates can enter via caveolae- or clathrin-mediated endocytosis depending on size/charge/surface chemistry. These parallel pathways are formulation-dependent and can be tuned with polymer coats (e.g., chitosan for mucoadhesion or HA for CD44 interactions). Figure 1F — Intracellular penetration & release. After entry, lipid exchange within endosomal and ER membranes and PC "flip-flop" facilitate hand-off of the active to intracellular lipids/proteins, increasing cytosolic availability at the site of action. The complex acts as a carrier, not a prodrug: pharmacology is unchanged; delivery is improved. Figure 1G — Dermal penetration

(topical route). On skin, phytosomes partition into stratum-corneum lipids, loosen locally ordered domains, and form a drug reservoir that sustains flux into viable epidermis. This benefits anti-inflammatory/antioxidant phytochemicals used in dermal indications. Figure 1H — Exposure–response amplification. By improving solubilization, permeability, and stability, phytosomes increase systemic or local exposure, shifting the exposure–response relationship upward (greater effect at the same dose) and/or leftward (same effect at a lower dose). The curve in the panel illustrates the practical outcome: dose-sparing or stronger effect without changing intrinsic potency.

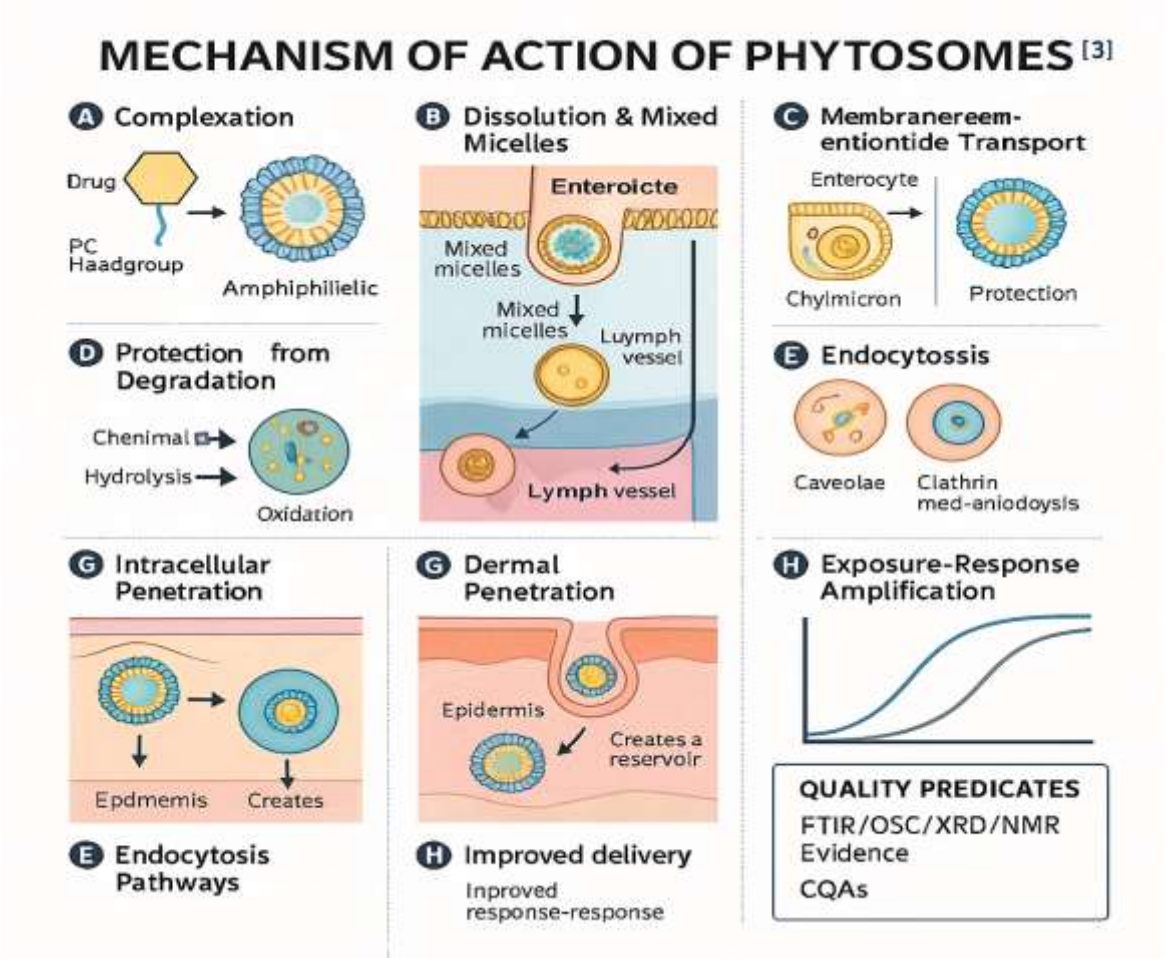

Figure 1: Drug–PC complexation creates an amphiphile that (i) co-solubilizes in bile-mixed micelles, (ii) partitions into enterocyte membranes and/or chylomicrons for partial first-pass bypass, (iii) protects against hydrolysis/oxidation, (iv) can enter by endocytosis and release intracellularly, (v) forms a dermal depot topically, and (vi) raises exposure, improving response at equal or lower doses. Confirmation requires FTIR/NMR/DSC/XRD evidence and control of CQAs**.**

4. Polymer add-ons for phytosomes: roles and typical use levels

The graphic is a quick "toolbox" of polymer options that can be added to phytosomes to solve specific delivery problems: chitosan/TMC gives cationic mucoadhesion (TMC remains soluble near neutral pH), hyaluronic acid (HA) increases hydration and viscosity, alginate/pectin provide pH-dependent gelation for GI/nasal control**,** carbomer offers pH-sensitive thickening and physical stability, PEG/DSPE-PEG forms a steric "stealth" corona to reduce opsonization (at higher cost), and PVP improves wetting/dissolution with some gastro-adhesion at low levels. Saccharide glass-formers like pullulan, dextran, and maltodextrin help dry-state/lyophilization stability (high-MW dextrans can add gastro-resistance). For GI targeting, HPMC/HPMCAS/HPMCP and Eudragit L/S (including RS/RL ionic grades) enable enteric or colon-triggered release, while PLGA/PCL (sometimes blended with PVP) create biodegradable matrices for sustained release as shown in figure 2. The central message: choose the polymer that matches the bottleneck—mucoadhesion, hydration, pH-triggered release, stealth, dissolution, viscosity/stability, or anatomical targeting—and use low percent loadings as a starting point before optimization. Phytosomes are stoichiometric drug–phosphatidylcholine (PC) complexes in which phenolic –OH/carbonyl groups engage PC's headgroup via H-bonding/ionic and π–π interactions, converting poorly membrane-compatible phytoconstituents into amphiphiles with high bilayer affinity—distinct from liposomes, which merely encapsulate solutes. Orally, the drug–PC complex disperses as colloids that co-assemble with bile salts/dietary lipids into mixed micelles, raising apparent solubility and maintaining a membrane-seeking state that enhances the lumen-to-epithelium gradient. At enterocytes, the PC anchor promotes partitioning into the apical membrane and transcellular diffusion; part of the dose associates with chylomicrons for lymphatic transport, elevating exposure (AUC, C_max) and mitigating first-pass loss, as shown for silybin, curcumin, and catechins versus non-complexed forms. Complexation also shields labile motifs from hydrolysis/oxidation and curbs aggregation/crystallization, while the PC matrix/reduced crystallinity in solids slows degradation to preserve the deliverable fraction during transit/storage. Beyond passive partitioning, nanoscale aggregates can enter via caveolae/clathrin pathways; subsequent lipid exchange in endosomal/ER membranes releases the active to the cytosol, with PC-mediated flip-flop/lateral diffusion easing intracellular hand-off. Topically, the amphiphilic complex partitions into and fluidizes stratum-corneum lipids, forming a reservoir that increases cutaneous deposition and sustains flux into viable epidermis—useful for anti-

inflammatory/antioxidant polyphenols [4]. Overall, phytosomes amplify pharmacodynamics by boosting effective biophase concentrations without altering receptor pharmacology, yielding more consistent, dose-normalized benefits. These gains require verified complexation (FTIR/NMR/DSC/XRD) and control of CQAs (size/PDI, ζ-potential, entrapment/drug content) with validated analytics; otherwise, systems regress to simple mixtures or unstable colloids, and the advantages erode.

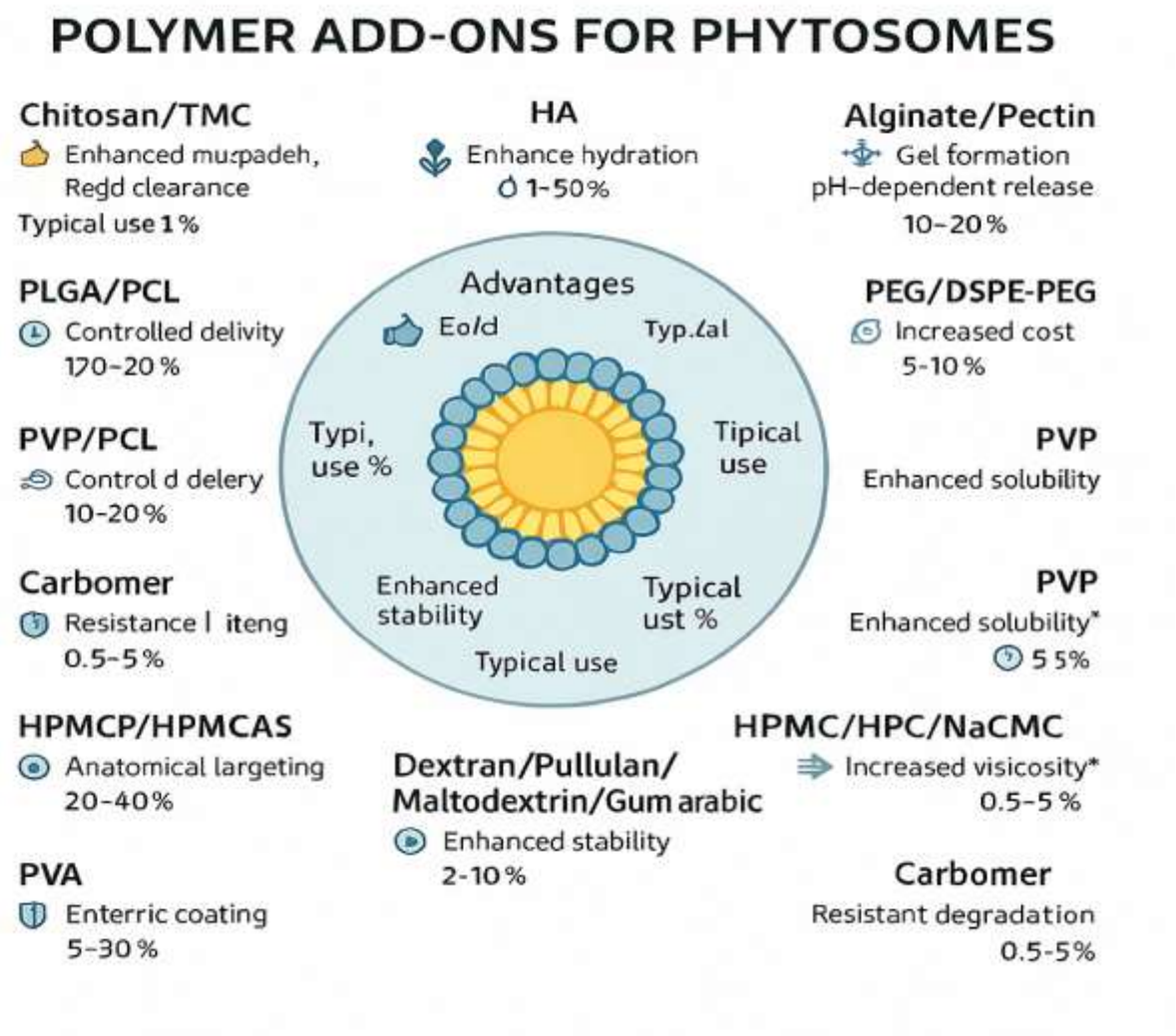

Figure 2. Polymer add-ons for phytosomes: primary roles and indicative use levels. Chitosan/TMC (mucoadhesion/permeation), hyaluronic acid (hydration/targeting), PEG/DSPE-PEG (steric stabilization), HPMC/HPC/NaCMC (viscosity/controlled release), carbomer (topical pH-gel), alginate/pectin (ionotropic gels, pH-triggered release), PLGA/PCL (sustained depots), PVA (film/coat), and dextran/pullulan/maltodextrin (spray/freeze-dry carriers). *Abbreviations:* TMC, trimethyl chitosan; HPMC/HPC/NaCMC, hydroxypropyl-/hydroxypropyl-methyl-/sodium carboxymethyl-cellulose; DSPE-PEG, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-PEG; PVA, polyvinyl alcohol; PLGA, poly(lactic-co-glycolic acid); PCL, poly(ε-caprolactone)

5. Phytosome loaded with natural products

Silybin (milk thistle) was the first widely studied phytosome and showed markedly higher oral exposure vs. silymarin in healthy volunteers [35]. Curcumin–phosphatidylcholine (Meriva®) has repeated clinical data in osteoarthritis showing improved symptoms with excellent tolerability [36]. Green-tea catechins (Greenselect® Phytosome) have human data for weight loss and for reducing weight-regain after lifestyle interventions [37,38]. Quercetin Phytosome® significantly increases human oral absorption in a randomized crossover PK study [39]. Resveratrol has been formulated as a phospholipid complex and combined with SMEDDS to enhance oral bioavailability in vivo [40]. Flavones from *Scutellaria* have multiple phospholipid-complex exemplars: baicalein (BaPC) shows improved dissolution/permeability and higher AUC in rats [41], and BaPC-SMEDDS enhances oral absorption and lymphatic transport [42]; a complementary study with baicalin PC likewise improved absorption metrics [43]. Berberine Phytosome® has randomized clinical data (e.g., in PCOS) suggesting better efficacy/tolerability than conventional berberine salts [44]. Ginkgo biloba phytosome has preclinical CNS/antioxidant evidence supporting functional activity in brain tissues [45]. Rutin phytosome improves transdermal permeation, supporting topical/dermal uses as summarized Table 2 [46].

Table 2: Phytosome loaded with natural products

Active (common name)	Phytosome formulation / brand	Route & dosage form	Study type & model	Key outcome(s)
Silybin (milk thistle)	Silybin–PC complex (IdB 1016)	Oral capsules	Human PK, healthy volunteers	↑ Oral exposure vs. silymarin/silybin control
Curcumin	Curcumin–PC (Meriva®)	Oral tablets/capsules	Clinical OA studies	Symptom improvement, good tolerability
Green-tea catechins	Greenselect® Phytosome	Oral capsules	Clinical obesity/weight-maintenance	↓ Body weight; better weight maintenance post-loss
Quercetin	Quercetin Phytosome®	Oral capsules	Human PK, crossover	↑ Oral absorption vs. standard quercetin
Resveratrol	Phospholipid complex + SMEDDS	Oral liquid/capsule	Animal PK	↑ Bioavailability vs. plain resveratrol

Baicalein	Baicalein–PC (matrix dispersion)	Oral solid	Animal PK & in-vitro	↑ Dissolution/permeation; ↑ AUC in rats
Baicalein	Baicalein–PC in SMEDDS	Oral liquid	Animal PK/lymphatic	↑ Oral absorption; ↑ lymphatic transport
Baicalin	Baicalin–PC + self-emulsifying microemulsion	Oral liquid	Animal PK	↑ Oral absorption vs. control
Berberine	Berberine Phytosome®	Oral tablets	RCT in PCOS	Better efficacy/tolerability vs. conventional salt
Ginkgo biloba extract	Ginkgo phytosome	Parenteral/PO (preclinical)	Rat brain models	Antioxidant activity in brain tissues
Rutin	Rutin phytosome	Topical/transdermal films/gels	In-vitro/ex-vivo skin	↑ Transdermal permeation; better deposition

6. Review of Preparation of Phytosome

Phytosomes are made by complexing a phytoconstituent with a phospholipid (most often phosphatidylcholine, PC) in roughly 1:1 to 1:2 molar ratios, using volatile, pharmaceutically acceptable solvents (e.g., ethanol, acetone, dichloromethane, dioxane) or co-solvent systems. Process selection governs complexation efficiency, particle size distribution, and solid-state features, which in turn drive performance; therefore each method should be paired with orthogonal analytics (FTIR/NMR, DSC, PXRD/XRD; plus size/PDI/ζ and drug content) to verify true complexation vs. a mere physical mixture [47–50].

6.1) Solvent-evaporation / thin-film (sometimes called "solvent-evaporation–hydration")

This is the most cited route. The drug and PC are co-dissolved (often with a trace of cholesterol), gently refluxed/mixed to allow hydrogen-bond/ionic/π–π interaction, and the solvent is evaporated under reduced pressure (rotavap). The resulting drug–PC complex film is then hydrated/dispersed (aqueous buffer), sometimes followed by probe/ bath sonication or extrusion to narrow size. Advantages: high reproducibility, scalable, compatible with many actives and solvents. Trade-offs: solvent handling and residual-solvent control; potential thermal stress if temperatures are not minimized [47,49–52]. Method variants are reported for single compounds (e.g., probucol-PLC, Centella asiatica extract–PLC) with FTIR/DSC/PXRD confirming complexation [51,52,56].

6.2) Anti-solvent (salting-out) precipitation: Here, drug and PC are co-dissolved in a mutual organic solvent and then anti-solvent (e.g., n-hexane) is added (or the organic phase is poured into

anti-solvent) to precipitate the complex. The solid is filtered and dried (vacuum oven/freeze-dry). Advantages: lower particle size and often higher EE% at modest energy input; solid product directly. Considerations: careful control of addition rate, temperature, and anti-solvent/drug–PC solubility window; some systems still need a brief reflux/mixing step pre-precipitation. Comparative studies and recent experimental reports highlight lower size and good stability from antisolvent routes versus simple solvent evaporation [49,53,54].

6.3) Slurry / reflux (co-solvent) complexation

In "slurry" or reflux-assisted methods, PC is swollen in a suitable solvent (or minimal solvent blend), the drug is added, and the mixture is stirred/refluxed for a defined time to drive stoichiometric adduct formation, followed by solvent removal and drying. This can reduce solvent volumes versus full thin-film runs and is practical for extracts as well as single molecules. It shows similar confirmatory signatures (FTIR shifts, DSC endotherm changes, PXRD haloing) when complexation is complete [47,49,52].

6.4) Co-grinding / kneading (low-solvent or solvent-free)

Mechanical energy (ball mill, mortar-pestle, planetary mill) is used to knead the drug and PC at set ratios; a minimal wetting agent (e.g., ethanol/water) may be misted to "knead". Advantages: solvent-minimized, potentially greener; useful for heat-labile actives. Limitations: risk of incomplete complexation and broader size/PDI unless followed by dispersion/size-reduction; still requires spectroscopic/thermal proof of complex formation. For small molecules (e.g., probucol), co-grinding has produced PLCs with improved dissolution and PK versus drug alone [52].

6.5) Freeze-drying (lyophilization) as a primary route or solid-state conversion

Some reports classify freeze-drying as a core preparation route: drug and PC are dissolved (aqueous/organic co-solvent), complex in solution, then the whole is lyophilized to a dry, redispersible complex. More commonly, lyophilization is used after solvent evaporation or anti-solvent precipitation to stabilize nanoscale dispersions, often with cryoprotectants (e.g., trehalose, mannitol). Advantages: excellent redispersibility and shelf-stability; caveats: cake morphology and residual-solvent checks are critical [47,49].

6.6) Spray-drying (solid conversion / powder engineering)

Solution or suspension of the drug–PC complex is spray-dried (optionally with carriers such as maltodextrin/pullulan) to obtain a free-flowing powder or granules for capsules/tablets. The approach is attractive for scale-up and direct compression, with good control on residual solvent

(due to short residence times). It may increase aggregate size on reconstitution unless protectants/surfactants are optimized [47,48].

6.7) Method hybridization (complex-in-SMEDDS / polymer-coated phytosomes)

Several successful systems embed the pre-formed drug–PC complex into SMEDDS/SEDDS (self-micro-emulsifying systems) to boost solubilization and lymphatic transport, or apply polymer shells (e.g., chitosan, hyaluronic acid) post-complexation for mucoadhesion/targeting. These hybrid routes build on any of the above complexation methods and show additive gains in permeability/PK and stability—e.g., baicalein-PC in SMEDDS; gingerol phytosome via antisolvent, then chitosan coating [53,54,42 in your earlier list; cited here as 53,54].

6.8) Supercritical fluid-assisted processes (emerging/adjacent)

While most phytosome complexes are prepared by solution routes, supercritical anti-solvent (SAS) and related supercritical methods—well-documented for lecithin systems and liposomes—are being explored to generate solvent-minimized, narrow-size powders. Evidence is robust for lecithin/liposome engineering, and reviews of phytosomes flag SCF routes as promising; applying SAS to pre-complexed drug–PC dispersions is a logical extension but still less common than solution methods (note: this is an inference from liposome/lecithin data and phytosome reviews). All preparation methods are summarised in Table 3[57–59].

Table 3: Different preparation methods of phytosome

Method	Key steps (at a glance)	Typical solvents / conditions	Drug:PC (mol)	Representative examples
Solvent-evaporation / thin-film	Co-dissolve drug + PC → mild reflux/mix → rotary-evaporate to dry film → hydrate (pH 6.8–7.4) → optional sonication/extrusion	Ethanol, acetone, DCM, dioxane; 40–60 °C; vacuum to remove solvent	1:1–1:2 (common)	Probucol-PLC; Curcumin-PC; *Centella* extract-PC
Anti-solvent precipitation	Co-dissolve drug + PC → add anti-solvent (or pour organics into anti-solvent) →	Mutual solvent (ethanol/acetone) + anti-solvent (e.g., n-hexane); controlled	1:1–1:2	Gingerol-phytosome (then chitosan coat); other herbals

	precipitate complex → filter/dry	addition 0–10 °C or RT		
Slurry / reflux co-solvent	Swell PC in minimal solvent → add drug → stir/reflux (≤60 °C) → remove solvent → dry	Ethanol or co-solvent blends; 1–4 h mixing	1:1–1:3 (extracts may vary)	Many extract PLCs (e.g., *Centella*)
Co-grinding / kneading	Dry blend drug + PC → ball-mill or mortar-knead (minimal misted solvent optional) → sieve	Solvent-minimized or solvent-free	1:1–1:2	Probucol PLC (co-grinding vs solvent)
Freeze-drying (primary route or conversion)	Form solution/dispersion of drug–PC complex → lyophilize with cryoprotectant	Aqueous/organic co-solvent; trehalose/mannitol; validated cycle	1:1–1:2	Used as post-step in many PLCs
Spray-drying (powder engineering)	Feed solution/suspension of complex (± carriers) → spray-dry → collect powder/granules	Alcoholic feeds; inlet 80–150 °C (fit to API); carriers: maltodextrin/pullulan	1:1–1:2	Multiple herbal PLCs in powdered form
Hybrid: complex-in-SMEDDS/SEDDS	Prepare drug–PC complex → dissolve in SEDDS preconcentrate → fill capsules → self-emulsify in GI	Oils/surfactants (e.g., Capryol, Cremophor)	1:1–1:2 (complex); SEDDS load optimized	Resveratrol-PC+SMEDDS; Baicalein-PC+SMEDDS
Polymer-coated phytosomes (post-processing)	Make phytosome → coat with polymer (e.g., chitosan, HA) via	Aqueous; chitosan (pH < 6.5), HA layering	Base complex typical	Chitosan-coated gingerol PLC

	electrostatic LbL → wash/stabilize			
Supercritical anti-solvent (SAS) / SCF-assisted (emerging)	Dissolve complex or precursors → SAS with $scCO_2$ → rapid precipitation of fine powders	$scCO_2$; co-solvent as needed; moderate T/P	As per complex	SCF for lecithin/liposomes; flagged for PLCs

7. Analytical review of phytosome

Phytosome analysis aims to (i) verify true drug–phospholipid complexation, (ii) define vesicle size/charge/morphology, (iii) quantify all components, (iv) characterize release, permeability and digestion behavior, and (v) ensure stability and method validity aligned to intended route of administration [60]. Confirming complexation relies on converging orthogonal tests: FTIR and ^1H/^13C-NMR show diagnostic shifts of carbonyl, phosphate, and aromatic/aliphatic signals versus simple physical mixtures; ^31P-NMR line-shape changes reveal headgroup environment in complexes or bilayers; DSC/XRPD/hot-stage microscopy distinguish complex-induced amorphization from mere co-precipitation; Job's plot/Benesi–Hildebrand or non-linear fits, and isothermal titration calorimetry quantify stoichiometry and binding thermodynamics; fluorescence polarity/anisotropy probes confirm relocation of the phytochemical into the phospholipid microenvironment [61–66]. Size and dispersity are first read by DLS (report scattering angle, temperature, viscosity/refractive index settings, attenuator state), mindful of multiple scattering at higher solids; number-weighted techniques such as NTA, TRPS, or AF4-MALS provide orthogonal distributions and expose large-particle tails; ζ-potential by electrophoretic light scattering should state pH and ionic strength and apply the appropriate Smoluchowski/Henry model [67–69]. Morphology and lamellarity are resolved by cryo-TEM (native hydration), with negative-stain TEM/SEM or AFM as qualitative complements; lamellar order is quantified by SAXS/SANS peak series and ^31P-NMR anisotropy; phase behavior relevant to release is mapped using DSC/WAXS together with Laurdan generalized polarization to track gel↔fluid transitions and membrane order [70–72]. Composition requires validated assays for both drug and lipids: LC–MS/MS or HPLC (UV/FL/CAD) with deliberate vesicle disruption during sample prep ensures recovery; phospholipids are measured via Bartlett phosphate assay, ^31P-NMR, or HPLC-ELSD for class profiles; PEG density (^1H-NMR or iodine method), cholesterol by GC-FID, and residual

solvents by headspace GC complete excipient control [73–75]. Encapsulation efficiency (EE%) is established by separating free from vesicle-associated drug using ultracentrifugation (report RCF/time/temperature), size-exclusion chromatography, dialysis with controlled sink, or AF4-MALS; mass balance (recovery) must be shown, and leakage should be followed over time in physiologic media using detergent-rupture controls, self-quenching dyes, or FRET de-quenching assays [76–77]. Release testing should mirror route: Franz/dialysis setups for topical and mucosal use, USP IV flow-through or adapted USP I/II for oral formulations; maintain true sink with minimal solubilizer to avoid micellar artifacts; model with Higuchi, Korsmeyer–Peppas, zero-order, or Weibull and compare against free drug and physical mixtures with full reporting of membrane area, agitation, and media composition [78–79]. Bioperformance proxies include PAMPA with phospholipid coatings, Caco-2/HT29-MTX or Calu-3 models (report TEER and mass balance) and reconstructed tissues for skin/oral mucosa; muco-interaction is quantified by QCM-D/mucin adsorption, multiple-particle tracking through mucus, and rotating-cylinder detachment; for oral products, pH-stat lipolysis with bile/pancreatic enzymes partitions drug among aqueous, oil, and precipitated phases to diagnose supersaturation and precipitation-inhibitor needs [80–82]. Stability programs should track physical drift of size/PDI/ζ under ICH long-term/accelerated conditions, dilution/agitation and freeze–thaw robustness; chemical stability monitors lipid peroxidation (peroxide/TBARS), lysolipid formation and drug degradation per ICH Q1A; drying strategies (lyophilization/spray-drying) use sugars (trehalose/sucrose/pullulan) to protect bilayers, with residual moisture (Karl Fischer), cake structure, glass transition (mDSC), and reconstitution size/EE% reported [83–85]. For parenteral/ocular prospects, add sterility testing, endotoxin by LAL, particulate matter (USP <788>), osmolality and pH; early biocompatibility screens include protein-corona profiling, complement activation (CH50), hemolysis, and RBC uptake to anticipate in-vivo interactions [86–87]. Imaging and biodistribution leverage fluorescent tracers (e.g., DiI/NBD-PE) with leakage-corrected quantitation and CLSM co-localization; mechanistic optics such as FRAP (fluidity) and FRET (fusion/leakage) plus live-cell TIRF/STED clarify uptake routes; label-free ToF-SIMS or Raman mapping can confirm tissue deposition when labels are undesirable [88–90]. All pivotal assays should be validated per ICH Q2(R2)/Q14 (specificity, range, linearity, accuracy, precision, LOD/LOQ, robustness, analytical target profile), and manuscripts should include a minimum dataset: full composition (% w/w), preparation conditions, raw DLS correlograms and ζ methods, representative cryo-TEM, validated

drug/phospholipid assays, EE% with separation details and mass balance, route-appropriate release/permeability/lipolysis, and a pre-specified stability plan with data-sharing statement for reproducibility as summarized in Table 4 [91–92].

Table 4: Analytical Review of Phytosome

Active (common name)	Branded / formulation name	Route & dosage form	Process & complexation analytics	Study type & model	Key outcomes (vs. non-complexed control)
Silybin (milk thistle)	Silybin–PC (IdB 1016 / Silipide®/Siliphos®)	Oral capsules	Slurry/solvent evaporation; complexation typically supported by FTIR/DSC in method papers (PK paper focused on exposure)	Human PK (healthy)	↑ oral exposure (AUC, Cmax) vs silymarin/silybin; first clinical PoC for phytosomes
Curcumin	Meriva® (curcumin–PC)	Oral tablets/capsules	Thin-film/solvent route; complexation evidence reported in foundational Meriva tech papers; trials focus on clinical endpoints	Clinical (OA)	Improved symptom scores and function with good tolerability over extended use
Green-tea catechins	Greenselect® Phytosome	Oral capsules	Lecithin complex (food-grade PC); manufacturing disclosures in brand monographs; trials focus on outcomes	Clinical (obesity; weight maintenance)	↓ body weight as diet adjunct; better weight maintenance post-loss
Quercetin	Quercetin Phytosome® (Quercefit®)	Oral capsules	Phospholipid complex; FTIR/DSC/XRD typically used in formulation papers; human PK paper emphasizes exposure	Human PK (crossover)	↑ oral absorption (exposure) vs standard quercetin
Resveratrol	Resveratrol–PC + SMEDDS (hybrid)	Oral liquid/capsule	Phospholipid complexation + self-microemulsifying system; FTIR/DSC commonly reported; in-vivo PK emphasized	Animal PK	↑ bioavailability vs plain resveratrol; lymphatic contribution suggested
Baicalein	Baicalein–PC (matrix dispersion)	Oral solid	Matrix-dispersion PC complex; FTIR/DSC/XRD confirm complexation	In-vitro + animal PK	↑ dissolution & permeability; ↑ AUC in rats
Baicalein (PC in	Baicalein–PC in SMEDDS	Oral liquid	PC complex embedded in SMEDDS; FTIR/DSC	Animal PK + lymphatic	↑ oral absorption, ↑ lymphatic

SMEDDS)			used; lymphatic transport assessed		transport vs non-SMEDDS
Baicalin	Baicalin–PC + self-emulsifying microemulsion	Oral liquid	Sequential PC complexation + SEDDS; FTIR/DSC reported	Animal PK	↑ oral absorption vs control
Berberine	Berberine Phytosome®	Oral tablets	PC complex (disclosed by brand); clinical paper focuses on outcomes	Clinical RCT (PCOS)	Better efficacy/tolerability vs conventional berberine salts
Ginkgo biloba extract	Ginkgo phytosome	Oral/parenteral (preclinical)	PC complex; antioxidant assays in tissues; mechanistic focus	Preclinical (rat brain)	↑ antioxidant activity in brain tissues
Rutin	Rutin phytosome	Topical film/gel/transdermal	Thin-film or solvent evaporation; FTIR/DSC/XRD show complexation	In-vitro/ex-vivo skin	↑ transdermal permeation & skin deposition vs free rutin

8. Summary

Phytosomes are not liposomes but stoichiometric adducts between plant actives and phosphatidylcholine (PC) that transform poorly permeable, oxidation-prone molecules into amphiphiles with high membrane affinity. Orthogonal signatures—FTIR/NMR shifts at phenolic and phosphate/carbonyl regions, DSC endotherm changes, and XRD peak attenuation—distinguish true complexation from a physical blend [3–7]. When CQAs are kept within pragmatic targets (size ~80–250 nm, PDI ≤ 0.30, $|\zeta| \geq 20–30$ mV, EE% ≥ 70%), the complex co-solubilizes with bile, partitions into enterocyte membranes, and can traffic partly via chylomicrons, which together raise dose-normalized AUC and C_max versus non-complexed comparators [4,5,8–10]. These same attributes reduce aqueous aggregation and shield labile motifs, supporting chemical and physical stability through GI transit and storage under ICH-style programs [11,12]. The preparation toolkit is broad—solvent-evaporation/thin-film, anti-solvent precipitation, slurry/reflux, co-grinding, and solid-state conversions by lyophilization or spray-drying—each influencing solid-state form and particle attributes that ultimately govern performance [47–50]. Hybrid strategies embed the drug–PC complex in SMEDDS/SEDDS to boost solubilization and lymphatic access, or apply polymer shells to add mucoadhesion, stealth, or enteric protection, without altering the drug's intrinsic pharmacology [22–29,32–34]. Across methods, credible reporting hinges on validated assays for drug and lipid content, robust EE% determinations with mass balance, and transparent DLS/ζ conditions, so that batches can be compared within and across

studies [73–79,91,92]. Polymer add-ons function as route-specific “problem solvers” rather than primary carriers. Cationic chitosan/TMC improves mucoadhesion and epithelial permeation but requires pH-aware titration to avoid flocculation or charge-related cytotoxicity [16–18]. HA imparts hydration and can engage CD44 while potentially reducing uptake at high negative ζ; poloxamers lower interfacial stress and, in the case of F127, enable thermogels that extend residence on nasal or dermal surfaces [19,26,27]. PEG/DSPE-PEG adds steric stabilization and lyo-robustness at the cost of possible anti-PEG/ABC effects and reduced cellular uptake; cellulose ethers and carbomer tune viscosity and pH-responsive gel strength for oral or topical formats; alginate/pectin and methacrylate/HPMC enterics deliver site-specific GI release; PLGA/PCL furnish sustained depots; saccharide glass-formers (dextran, pullulan, maltodextrin) convert dispersions to re-dispersible powders with good processability [20,21,22–25,29–33]. These options are summarized conceptually in Figure 1 and operationally in Table 1. Human pharmacokinetic data provide early translational anchors. Silybin–PC (IdB 1016) consistently increases oral exposure versus silymarin/silybin controls in healthy volunteers, validating the mechanistic expectation that PC anchoring promotes transcellular permeation and partial lymphatic uptake [6,10]. Quercetin Phytosome® demonstrates higher human absorption in crossover designs, and curcumin–PC (Meriva®) shows symptom improvement and good tolerability in osteoarthritis studies, implying that PK gains can translate into clinically interpretable effects for inflammatory indications [9,13,14,39]. Green-tea catechin phytosomes (Greenselect®) report beneficial effects on weight loss and weight-maintenance when used as lifestyle adjuncts, suggesting utility for metabolic endpoints where modest, consistent exposure improvements matter [37,38]. Preclinical programs align with this pattern. Resveratrol–PC, especially when embedded in SMEDDS, increases bioavailability and hints at lymphatic contributions; baicalein and baicalin complexes improve dissolution/permeation and rat AUC, with SMEDDS hybrids further enhancing uptake and lymphatic transport [40–43]. In niche applications, berberine phytosome shows better efficacy and tolerability in an RCT in PCOS compared with conventional salts, while ginkgo phytosome improves antioxidant readouts in brain tissues, and rutin phytosomes increase transdermal deposition—together illustrating the breadth of routes and tissues amenable to the platform [44–46]. Though heterogeneous in design, these studies collectively support the central claim that verified drug–PC complexation, plus fit-for-purpose polymers and dosage-form engineering, can deliver reproducible exposure gains and, in

select cases, clinical signals (Table 2). A rigorous analytical battery is essential to separate genuine complexes from unstable mixtures. FTIR and NMR (including ^31P for headgroup microenvironment) should be interpreted alongside DSC/XRPD and, where possible, Job's plots or ITC to quantify stoichiometry and binding energetics [61–66]. Size metrics should include instrument settings and media properties (angle, viscosity/RI, temperature, attenuator state) to avoid non-comparable DLS outputs; number-weighted techniques (NTA, TRPS, AF4-MALS) help reveal large-particle tails that drive instability [67–69]. Cryo-TEM and SAXS/SANS address morphology and lamellarity; route-matched release/permeation tests (Franz/dialysis for topical and mucosal, USP IV or adapted I/II for oral) must maintain true sink and include appropriate comparators (free drug, physical mixture, non-complexed reference) [70–72,78,79]. Stability programs should track both physical drift (size/PDI/ζ over dilution, agitation, freeze–thaw) and chemical liabilities (lipid peroxidation, lysolipid formation, drug degradation) under ICH Q1A(R2) conditions, with reconstitution performance after lyo/spray-dry explicitly reported [83–85]. The literature base remains fragmented, with frequent under-reporting of PC source, purity, and fatty-acid profile that influence packing, oxidation risk, and membrane behavior [4,5,8]. Many papers specify drug:PC ratios empirically without thermodynamic rationale, and the level of complexation proof varies—from single-technique inferences to robust orthogonal confirmation—making cross-study comparisons uncertain [4,6,7,11]. EE% determinations sometimes lack validated phase-separation and mass-balance checks, while DLS results are reported without key instrument/media parameters, obscuring interpretability of size and PDI [67–77]. Stability is inconsistently addressed: accelerated and long-term ICH programs with stability-indicating assays are uncommon, and lipid oxidation or lysolipid formation is rarely quantified systematically [83–85]. Clinically, the portfolio is narrow, sample sizes are modest, durations are short, and head-to-head trials versus alternative enabling platforms (liposomes, SEDDS without complexation, polymeric micelles) are rare; safety nuances such as anti-PEG immunogenicity, complement activation, and excipient leachables remain under-characterized in repeat-dose settings [22–25,86,87]. Standardization should be the immediate priority. Adopting a minimum dataset—complete composition (% w/w), PC grade and fatty-acid profile, justified drug:PC stoichiometry, raw DLS correlograms and ζ methodology with pH/ionic strength, orthogonal complexation proof (FTIR/NMR/DSC/XRD), validated drug/lipid assays, EE% with separation details and recovery, route-appropriate release/permeation, and a pre-specified ICH-aligned stability plan—would

allow reproducible comparisons and meta-analyses [91,92]. Publishing spectra, micrographs, and raw PK tables as open supplements would further accelerate verification and regulatory confidence. Mechanistic biopharmaceutics should be deepened beyond high-level PK. Coupled in-vitro lipolysis–permeation models, chylomicron-flow blocking or lymph-cannulation studies, and PBPK models parameterized with measured bile/food effects can quantify the contributions of micellar solubilization, membrane partitioning, and lymphatic transport to exposure [80–82]. For topical/dermal use, linking cryo-TEM/SAXS-derived structure and in-skin chemical imaging (Raman/ToF-SIMS) to finite-dose Franz data would tighten the chain of evidence from deposition to effect. Clinical programs should expand in indication breadth and methodological rigor. Multi-arm, dose-normalized RCTs that compare phytosomes to non-complexed forms and to state-of-the-art alternatives (e.g., SEDDS alone) are needed to attribute benefits specifically to complexation. Trials should incorporate exposure–response analyses, food-effect characterization, and patient-relevant endpoints over adequate durations, while systematically capturing safety markers relevant to lipids and polymers (e.g., complement activation, anti-PEG antibodies, lipid peroxidation products). From a CMC and scale-up perspective, Quality-by-Design with factorial/Box–Behnken designs can define a defensible design space around drug:PC ratio, solvent/hydration conditions, and post-processing, supported by PAT for solvent removal and particle attributes. Continuous powder engineering (spray-dry) and emerging supercritical anti-solvent routes warrant exploration for greener, scalable conversions, provided complexation integrity is preserved [57–59]. Polymer innovation should include anti-PEG alternatives (polysarcosine, zwitterionic coronas), tunable muco-interactions (muco-inert vs mucoadhesive layering), and systematic immunocompatibility profiling to derisk repeat dosing.

9. Conclusions

Taken together, the compiled evidence supports a coherent process–structure–performance story: when phytochemicals are truly complexed to PC and manufactured within a controlled CQA envelope, they exhibit better solubilization, membrane partitioning, and chemical resilience that translate into meaningful PK gains and, for some actives, clinical benefits. Polymers and dosage-form engineering do not replace the complex but ensure it survives processing, transit, and the target route’s constraints. The platform’s promise is clear for several canonical actives (silybin, curcumin, catechins, quercetin) and plausible for many others, yet the field will advance faster with transparent analytics, ICH-aligned stability, scale-aware process control, and head-to-head

clinical trials that isolate the contribution of complexation. If these standards are adopted, phytosomes are well-positioned to become a reliable, generalizable approach for translating plant-derived actives from compelling in-vitro biology to consistent human exposure and effect.

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