

From Phytochemical to Phytosome: A Critical Evaluation of Phospholipid Complexation for Improving the Bioavailability of Natural Compounds with Antidiabetic Potential

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ABSTRACT

Natural phytochemicals represent an important source of bioactive molecules with potential applications in the management of metabolic disorders. Numerous compounds, including berberine, curcumin, quercetin, silybin, hesperidin, catechins and arbutin, have demonstrated pharmacological properties relevant to glucose and lipid homeostasis. However, the pharmaceutical development of many phytochemicals is restricted by poor aqueous solubility, inadequate membrane permeability, gastrointestinal instability, extensive metabolism and low oral bioavailability. Phospholipid complexation, commonly referred to as phytosome technology, has emerged as a strategy for overcoming selected biopharmaceutical limitations of plant-derived compounds. In phytosomes, phytoconstituents interact with phospholipids, particularly phosphatidylcholine, resulting in a lipid-compatible complex that may alter molecular organization, dissolution, membrane interaction and oral absorption. This review critically evaluates the scientific progression from free phytochemicals to phospholipid complexes, with emphasis on compounds possessing antidiabetic potential. The molecular basis of phytochemical–phospholipid association, selection of phospholipids, preparation strategies, critical material and process variables, Quality by Design principles, characterization approaches and mechanisms responsible for enhanced bioavailability are discussed. Evidence from representative compounds, including berberine, quercetin, curcumin and silybin, is considered from a pharmacokinetic rather than purely pharmacological perspective. Particular attention is given to the distinction between improved formulation characteristics and demonstrated enhancement of systemic bioavailability. The review identifies major gaps in current phytosome research, including inconsistent terminology, incomplete structural characterization, lack of standardized formulation criteria, inadequate correlation between critical quality attributes and pharmacokinetic performance, scale-up difficulties and limited clinical translation. Arbutin is discussed as an emerging candidate for phospholipid-based delivery because of its reported metabolic and glucose-regulatory potential and the need for improved pharmaceutical strategies. Future phytosome development should move from empirical formulation toward mechanism-based, Quality by Design-driven development in which molecular structure, phospholipid selection, complexation, critical quality attributes and pharmacokinetic performance are systematically connected. [1,2,4,8-13,18]

Keywords: phytosome; phospholipid complex; phytochemical; bioavailability; antidiabetic phytochemicals; phosphatidylcholine; pharmacokinetics; Quality by Design; arbutin; drug delivery.

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1. Introduction

The increasing prevalence of metabolic disorders has stimulated interest in therapeutic strategies capable of addressing multiple pathological processes associated with diabetes mellitus. Plant-derived phytochemicals are particularly attractive because many possess antioxidant, anti-inflammatory, glucose-regulatory, lipid-modulating and insulin-sensitizing properties. However, pharmacological activity demonstrated for a natural compound does not necessarily translate into effective oral therapy. [2-4]

A major obstacle is poor biopharmaceutical performance. Many phytochemicals exhibit limited aqueous solubility, inadequate intestinal permeability, chemical instability, gastrointestinal degradation, extensive metabolism or active efflux. These factors may result in low and variable systemic exposure despite potentially favorable pharmacological properties. Thus, the development of natural products requires simultaneous consideration of both pharmacological activity and pharmaceutical availability. [1-3]

Several delivery technologies have been investigated to overcome these limitations, including liposomes, nanoemulsions, micelles, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, nanocrystals and self-emulsifying systems. Phospholipid complexation, commonly described as phytosome technology, represents a distinct approach in which the phytoconstituent interacts with phospholipids to produce a lipid-compatible complex. [3,15]

The phytosome concept is not new. Earlier studies established the potential of phosphatidylcholine complexes to improve the absorption of poorly bioavailable plant constituents. More recent reviews have expanded the field to include applications in metabolic disorders, diabetes, inflammation, cardiovascular diseases and other conditions. [1,2,14]

Consequently, a conventional review describing the preparation and applications of phytosomes would have limited novelty. The present review adopts a critical formulation perspective and focuses on the relationship: [1,2]

Phytochemical structure → phospholipid complexation → critical formulation attributes → oral bioavailability

The review further considers whether currently available evidence is sufficient to identify formulation characteristics capable of predicting improved systemic exposure. [1,2,7]

2. Biopharmaceutical Barriers to Oral Delivery of Phytochemicals

The oral fate of a phytochemical can be simplified as:

Dosage form → dissolution → gastrointestinal stability → intestinal permeability → absorption → metabolism → systemic circulation → tissue distribution.

Failure at any stage can limit therapeutic exposure. [1,2]

2.1 Poor aqueous solubility

Many natural compounds contain aromatic rings and multiple hydrogen-bonding groups that promote strong intermolecular interactions and crystalline packing. Consequently, dissolution in gastrointestinal fluid may be slow or incomplete. [1,2]

Poor solubility is particularly important because increasing the administered dose does not necessarily result in a proportional increase in absorbed drug. [1,2]

2.2 Limited membrane permeability

Intestinal epithelial membranes are predominantly lipidic. Highly hydrophilic phytochemicals may demonstrate inadequate membrane partitioning, whereas highly lipophilic molecules may dissolve poorly in aqueous gastrointestinal fluids. [1,2]

Therefore, successful oral delivery requires an appropriate balance between aqueous dispersibility and membrane compatibility. [1,2]

2.3 Gastrointestinal instability

Some phytochemicals are susceptible to:

- hydrolysis;
- oxidation;
- enzymatic degradation;
- pH-dependent degradation; and
- interaction with gastrointestinal components.

Protection from these processes may increase the fraction of active compound available for absorption. [1,2]

2.4 First-pass metabolism

Extensive intestinal and hepatic metabolism can substantially reduce the concentration of parent compounds in systemic circulation. Polyphenolic compounds are frequently subjected to glucuronidation, sulfation and other metabolic pathways. [2,3]

2.5 Efflux and transporter-mediated limitations

Intestinal transporters can further influence the absorption of phytochemicals and contribute to interindividual differences in exposure. [2,3]

These limitations provide the pharmaceutical rationale for phospholipid-based delivery. [1,2,14]

3. Phospholipid Complexation and the Phytosome Concept

Phytosomes are generally described as complexes formed between phytoconstituents and phospholipids, particularly phosphatidylcholine. [1,2,14]

Phosphatidylcholine possesses a hydrophilic polar head and hydrophobic fatty-acid chains.

Phytoconstituents containing hydroxyl, carboxyl or amino groups can interact with the polar region of phospholipids through hydrogen bonding and other intermolecular forces. [1,2,14]

A simplified representation is:

Phytochemical + phosphatidylcholine → phytochemical–phospholipid complex

The interaction can alter:

- molecular organization;
- crystallinity;
- polarity;
- lipid compatibility;
- dissolution;
- membrane interaction; and
- potentially gastrointestinal absorption.

An important distinction should be made between phytosomes and liposomes. In conventional liposomes, an active compound is encapsulated or partitioned within a phospholipid vesicular system. In phytosomes, the phytoconstituent forms an integral part of the phospholipid complex through molecular interactions. [1,2,14]

Thus, phytosomes should not simply be regarded as "liposomes containing herbal compounds." [1,2,14]

4. Why Phosphatidylcholine?

Phosphatidylcholine is the most widely investigated phospholipid for phytosome development. [1,2,14] Its advantages include:

- amphiphilic nature;
- membrane compatibility;
- biocompatibility;
- ability to interact with polar phytoconstituents;
- availability from natural sources; and
- established use in pharmaceutical and nutritional formulations.

However, the selection of phosphatidylcholine should not be considered universal. [1,2,5]

Important phospholipid variables include:

- purity;
- phosphatidylcholine content;
- fatty-acid composition;
- degree of saturation;
- oxidation stability;
- source; and
- interaction potential with the selected phytochemical.

The chemical structure of the phytochemical should therefore guide phospholipid selection. [1,2]

5. Molecular Determinants of Phospholipid Complexation

Not all phytochemicals possess the same capacity to form stable phospholipid complexes. [1,2]

Important molecular characteristics include:

- molecular weight;
- polarity;
- lipophilicity;
- hydrogen-bonding capacity;
- number of hydroxyl groups;

- carboxyl or amino groups;
- aromaticity;
- crystallinity; and
- three-dimensional molecular structure.

The presence of suitable functional groups can promote intermolecular interactions with phospholipid head groups. [1,2,14]

This provides a strong rationale for developing structure–complexation relationships. [1,2]

For example, the formulation strategy used for highly lipophilic curcumin cannot automatically be transferred to a more hydrophilic glycoside such as arbutin. [1,2,18]

This is an important area where current phytosome literature remains insufficiently predictive. [2,5,6]

6. Preparation of Phospholipid Complexes

Several approaches have been reported for preparing phytosomes. [1,2,14]

6.1 Solvent evaporation

The phytochemical and phospholipid are dissolved in an appropriate solvent system and mixed under controlled conditions. The solvent is subsequently removed, producing the complex. [1,2,14]

This remains one of the commonly used laboratory approaches. [1,2]

6.2 Antisolvent precipitation

The phytochemical and phospholipid are dissolved in one solvent and subsequently introduced into an antisolvent to induce precipitation. [1,2]

6.3 Thin-film methods

The components are dissolved in an organic solvent followed by solvent evaporation to produce a thin film, which can subsequently undergo further processing. [1,2]

6.4 Self-assembly

Certain phytochemical–phospholipid complexes can undergo spontaneous organization under appropriate solvent and concentration conditions. [1,2]

Berberine-phospholipid phytosomes, for example, have been prepared using rapid solvent evaporation followed by self-assembly. [8]

7. Critical Material and Process Variables

The final performance of a phytosome depends on both material characteristics and manufacturing conditions. [1,2,7]

Critical material attributes

- phytochemical purity;
- phospholipid purity;
- phytochemical:phospholipid ratio;
- phospholipid type;
- solvent characteristics;
- phytochemical particle characteristics.

Critical process parameters

- temperature;
- mixing time;
- agitation;
- solvent evaporation rate;
- concentration;
- sonication;

- drying conditions.

These variables can influence:

- complexation efficiency;
- particle size;
- PDI;
- surface charge;
- crystallinity;
- dissolution;
- stability; and
- bioavailability.

Importantly, the optimal formulation should not simply maximize one parameter, such as complexation efficiency. The objective is to obtain an overall formulation profile that provides adequate stability and reproducible bioavailability. [2,7]

8. Quality-by-Design Approach

The application of **Quality by Design (QbD)** offers an important opportunity to improve phytosome development. [7]

A QbD framework can be represented as:

Quality Target Product Profile

↓

Risk assessment

↓

Critical Material Attributes

Critical Process Parameters

↓

Design of Experiments

↓

Critical Quality Attributes

↓

Optimized formulation

Recent literature has specifically proposed integration of QbD into phytosomal development, emphasizing systematic risk assessment and experimental design rather than conventional trial-and-error optimization. [7]

Potential CQAs include:

Critical Quality Attribute	Importance
Particle size	Dispersion and dissolution
PDI	Size uniformity
Zeta potential	Physical stability
Complexation efficiency	Degree of phytochemical–phospholipid association
Phytochemical content	Dose consistency
Crystallinity	Molecular organization
Morphology	Structural integrity
Dissolution	Pharmaceutical performance
Residual solvent	Product safety

Chemical stability	Shelf-life
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Source basis: [2,7].

QbD therefore provides a framework through which formulation variables can be quantitatively linked to product performance. [7]

9. Characterization: Beyond Particle Size

One of the weaknesses of many phytosome reports is the tendency to rely on a small number of characterization techniques. [2]

A scientifically robust characterization strategy should combine complementary techniques. [2]

9.1 Particle size and PDI

Dynamic light scattering provides information on particle size and distribution. [2]

Particle size may affect:

- surface area;
- dissolution;
- dispersion;
- aggregation;
- physical stability.

9.2 Zeta potential

Zeta potential provides information about surface charge and can assist in assessing colloidal stability. [2]

9.3 FTIR spectroscopy

FTIR can identify changes in functional-group vibrations following phytochemical–phospholipid interaction. [2,14]

However, FTIR alone should not be considered definitive evidence of complex formation. [2,14]

9.4 Differential scanning calorimetry

DSC provides information regarding thermal transitions and changes in physical state. [2]

9.5 X-ray diffraction

XRD can determine changes in crystallinity. [2,14]

A reduction in characteristic crystalline peaks may indicate decreased crystallinity or conversion to a less ordered state. [2,14]

9.6 Electron microscopy

SEM and TEM can provide morphological information. [2,14]

9.7 NMR

NMR may provide stronger molecular-level evidence for interactions between phytochemicals and phospholipids. [2,14]

A comprehensive 2021 review emphasized the importance of combining formulation principles and characterization methods rather than relying on a single analytical technique. [2]

10. The Critical Distinction: Formulation Improvement Versus Bioavailability Improvement

This distinction should be central to the review.

A formulation may demonstrate:

↓ **particle size**

↑ **dissolution**

altered FTIR spectrum

altered DSC profile

↓ crystallinity

without necessarily demonstrating increased systemic bioavailability. [2,8-13]

The strongest evidence pathway is:

Complex formation → improved pharmaceutical characteristics → improved absorption → increased systemic exposure [2,8-13]

The final step requires pharmacokinetic measurements such as:

- C_{max};
- T_{max};
- AUC;
- half-life;
- clearance; and
- relative bioavailability.

Therefore, the statement "**phytosome improves bioavailability**" should ideally be supported by pharmacokinetic data rather than inferred solely from physicochemical characterization. [2,8-13]

11. Pharmacokinetic Evidence for Representative Phytochemicals

11.1 Berberine

Berberine has considerable pharmacological interest but poor gastrointestinal absorption and low oral bioavailability. [8,13]

Yu et al. developed berberine-phospholipid-complex phytosomes using rapid solvent evaporation and self-assembly. The formulation demonstrated approximately 85% entrapment efficiency and a nanoscale particle size. The authors reported approximately threefold enhancement of oral bioavailability compared with conventional berberine and improved metabolic effects in diabetic mice. [8]

This study is important because it connects formulation development with pharmacokinetic improvement. [8]

More recently, a food-grade berberine phytosome formulation was evaluated in healthy human volunteers. The study reported substantially greater systemic exposure, with AUC approximately tenfold higher on a molar basis than unformulated berberine under the study conditions. [13]

Thus, berberine provides an important example of translation from experimental formulation to human pharmacokinetic investigation. [8,13]

11.2 Quercetin

Quercetin has poor oral absorption despite extensive pharmacological interest. [9]

Riva et al. investigated a lecithin-based Quercetin Phytosome in healthy volunteers using a randomized crossover pharmacokinetic design. The formulation produced substantially greater oral absorption than unformulated quercetin. [9]

The study is particularly relevant because it demonstrates that phospholipid complexation can improve systemic exposure in humans. [9]

However, increased plasma exposure should not automatically be interpreted as increased clinical efficacy. [9]

11.3 Silybin

Silybin-phosphatidylcholine is one of the most extensively investigated phytophospholipid systems. [10-12]

Early human pharmacokinetic studies demonstrated substantially greater plasma exposure following administration of the silybin-phosphatidylcholine complex compared with conventional silymarin. [10]

A later randomized crossover study involving healthy volunteers also reported higher plasma silybin concentrations following administration of a silybin-phosphatidylcholine complex compared with conventional silymarin tablets. [11,12]

These studies provide some of the strongest human evidence supporting the pharmacokinetic advantage of phospholipid complexation. [10-12]

11.4 Curcumin

Curcumin presents multiple formulation challenges, including poor aqueous solubility, instability and extensive metabolism. [2,14]

Phospholipid formulations have been investigated as one approach to improving curcumin exposure. However, curcumin is also an excellent example of why formulation comparison is important: multiple delivery technologies can substantially modify its pharmacokinetics. [2,14]

Therefore, a phytosome should ideally be compared not only with the free phytochemical but also with an appropriate physical mixture or alternative formulation when the objective is to establish a formulation-specific advantage. [2,14]

12. Comparative Evidence

Table 1. Representative phytochemical–phospholipid systems and bioavailability evidence

Phytochemical	Phospholipid system	Evidence type	Reported bioavailability/exposure finding	Major or significance
Berberine	Phospholipid complex/phytosome	Animal PK	~3-fold increase reported	Demonstrates formulation–PK relationship

Berberine	Food-grade phytosome	Human PK	AUC substantially higher; approximately 10-fold on molar basis reported	Human translational evidence
Quercetin	Lecithin phytosome	Human PK	Substantial increase in oral absorption	Human proof-of-concept
Silybin	Phosphatidylcholine complex	Human PK	Higher plasma exposure than conventional silymarin	Established phospholipid-complex model
Curcumin	Phospholipid formulation	Human/experimental PK	Improved exposure reported for selected formulations	Demonstrates formulation dependence
Arbutin	Phospholipid complex	Emerging	Requires systematic PK evaluation	Important research oppo

				rtunity
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Source basis: [8-13].

The evidence demonstrates that **phospholipid complexation can improve exposure**, but the magnitude of improvement varies substantially among compounds and formulations. [8-13]

13. Natural Compounds with Antidiabetic Potential: Why Formulation Matters

The relevance of phytosome technology to diabetes does not arise simply because phytosomes are "antidiabetic." [2,3]

Rather, many phytochemicals with metabolic potential suffer from pharmaceutical limitations that can restrict their development. [2,3,15]

Table 2. Biopharmaceutical rationale for selected antidiabetic phytochemicals

Phytochemical	Class	Major pharmaceutical challenge	Formulation rationale
Berberine	Alkaloid	Low oral bioavailability	Improve oral exposure
Curcumin	Polyphenol	Poor solubility and metabolism	Improve dissolution and absorption
Quercetin	Flavonoid	Poor oral absorption	Improve membrane interaction
Silybin	Flavonolignan	Low bioavailability	Improve gastrointestinal absorption
Hesperidin	Flavonoglycoside	Solubility/permeability limitations	Improve lipid compatibility

Catechins	Flavan-3-ols	Stability and metabolism	Improve oral delivery
Resveratrol	Stilbene	Rapid metabolism and low systemic exposure	Improve exposure
Arbutin	Phenolic glycoside	Delivery and formulation challenges	Explore phospholipid complexation

Source basis: [2,3,8-12,18].

This formulation-centered approach prevents the review from becoming another general discussion of antidiabetic phytochemicals. [2,3]

14. Arbutin: An Emerging Candidate for Phytosomal Development

Arbutin is a naturally occurring hydroquinone glycoside that has attracted increasing interest because of its antioxidant, anti-inflammatory and metabolic properties. [18]

A comprehensive review published in 2024 examined arbutin's chemistry, pharmacokinetics, pharmacological properties, toxicity and emerging formulation approaches. [18]

Experimental research has also reported beneficial effects of arbutin in a high-fat diet/streptozotocin-induced diabetic rat model, including effects on hyperglycemia, dyslipidemia, oxidative stress and PPAR γ -related metabolic pathways. [18]

However, the important formulation question is different:

Can phospholipid complexation produce a reproducible improvement in the oral biopharmaceutical performance of arbutin?

Arbutin differs structurally from highly lipophilic phytochemicals such as curcumin. Its glycosidic structure contributes to a more hydrophilic profile. Consequently, an arbutin phytosome should not simply be developed on the assumption that the mechanism observed with curcumin or silybin will be identical. [18,2]

A scientifically interesting research direction is therefore to investigate:

arbutin molecular structure

↓

phospholipid interaction

↓

complexation efficiency

↓

change in crystallinity/thermal behavior

↓

membrane compatibility

↓

oral exposure

This provides a stronger scientific rationale for arbutin phytosome development than simply describing arbutin as an antidiabetic phytochemical. [18,2]

15. Formulation–Bioavailability Relationship

A major unresolved issue is whether commonly measured formulation parameters can predict pharmacokinetic improvement. [2,7]

Theoretically:

Higher complexation efficiency

→ more phytochemical associated with phospholipid

→ altered molecular organization

→ improved membrane interaction

→ potentially greater absorption.

Similarly:

Reduced particle size

→ increased surface area

→ potentially improved dispersion/dissolution

→ potentially greater absorption.

However, these relationships are not necessarily linear. [2,7]

For example, excessive phospholipid content may increase formulation size or alter stability. Extremely small particles may also aggregate if surface stabilization is inadequate. [2,7]

Therefore, the formulation objective should not be:

"Make the smallest possible phytosome."

Instead, it should be:

"Identify the optimum combination of molecular complexation, particle characteristics, stability and biopharmaceutical performance." [2,7]

This is where QbD can substantially strengthen future research. [7]

16. Stability of Phytosomal Systems

Long-term stability is essential for pharmaceutical translation. [2,5]

Potential instability mechanisms include:

- phospholipid oxidation;
- phospholipid hydrolysis;
- aggregation;
- particle growth;
- phytochemical degradation;
- loss of molecular association;
- changes in crystallinity.

Stability studies should therefore evaluate both **chemical and physical attributes**. [2,5]

Recommended parameters include:

- phytochemical assay;
- degradation products;
- particle size;
- PDI;
- zeta potential;
- appearance;
- moisture;
- dissolution;

- complexation characteristics.

The use of antioxidants, appropriate packaging, controlled moisture and oxygen exposure may be considered depending on formulation composition. [2,5]

17. Scale-Up and Manufacturing Challenges

The successful preparation of a phytosome at laboratory scale does not guarantee reproducible large-scale manufacture. [2,5,7]

Scale-up can change:

- mixing efficiency;
- heat transfer;
- solvent evaporation;
- mass transfer;
- drying;
- particle formation.

Natural raw materials add another layer of complexity because phytochemical content can vary according to:

- plant species;
- geographical origin;
- cultivation conditions;
- harvest time;
- extraction method;
- storage.

Therefore, standardization of the active phytochemical and phospholipid components is essential. [2,5,7]

Future industrial development should incorporate: **raw-material standardization → controlled manufacturing → in-process controls → CQAs → stability → pharmacokinetic consistency.** [2,5,7]

18. Regulatory Considerations

Phytosomal products may be developed as pharmaceuticals, nutraceuticals, botanical products or dietary supplements, depending on their intended use and jurisdiction. [2,5,6]

This creates challenges regarding:

- product classification;
- quality standards;
- safety requirements;
- clinical evidence;
- manufacturing standards;
- labeling.

The fact that a formulation contains a naturally derived compound does not eliminate the requirement for reproducible quality. [2,5,6]

A commercially viable phytosomal product should demonstrate:

1. consistent phytochemical content;
2. reproducible phospholipid composition;
3. validated analytical methods;
4. controlled manufacturing;
5. acceptable stability;
6. appropriate safety evidence; and
7. evidence supporting the proposed health or therapeutic claim. [2,5,6]

19. Major Research Gaps

Despite substantial progress, several important gaps remain. [2,5-7]

19.1 Lack of a standardized definition

The terms *phytosome*, *phytophospholipid complex*, *phospholipid complex* and *nanophytosome* are sometimes used interchangeably despite differences in formulation architecture. [2,5,6]

19.2 Insufficient molecular characterization

Particle size and FTIR are frequently reported, but molecular-level structural evidence remains comparatively limited. [2,6,7]

19.3 Weak CQA–PK relationships

Few studies systematically establish which CQAs best predict increased systemic exposure. [2,7]

19.4 Inconsistent formulation ratios

There is no universal phytochemical:phospholipid ratio applicable to all natural compounds. [2,5,7]

19.5 Limited human pharmacokinetic studies

Although human data exist for selected compounds such as quercetin, berberine and silybin, the majority of phytochemicals remain insufficiently characterized pharmacokinetically. [2,6,7]

19.6 Limited scale-up evidence

Many published systems remain at laboratory-development stage. [2,5,7]

19.7 Inadequate long-term stability data

Physical and chemical stability remains an important consideration for commercial development. [2,5]

19.8 Insufficient comparative studies

Future studies should ideally compare:

free phytochemical

vs

physical phytochemical–phospholipid mixture

vs

optimized phospholipid complex

This would help determine whether the observed benefit originates from true complexation or simply from the presence of phospholipid. [2,7]

20. Future Perspectives

The next generation of phytosome research should move toward **predictive formulation science.** [2,7]

A proposed development framework is:

Stage 1 — Molecular screening

Determine:

- polarity;
- hydrogen-bonding capacity;
- lipophilicity;
- molecular size;
- functional groups.

↓

Stage 2 — Phospholipid selection

Evaluate:

- phosphatidylcholine type;
- purity;
- fatty-acid composition;
- compatibility.

↓

Stage 3 — QbD formulation

Identify:

- CMAs;
- CPPs;
- CQAs.

↓

Stage 4 — Advanced characterization

Combine:

- FTIR;
- DSC;
- XRD;
- NMR;
- particle-size analysis;
- microscopy.

↓

Stage 5 — Biopharmaceutical assessment

Evaluate:

- dissolution;
- stability;
- permeability;
- pharmacokinetics.

↓

Stage 6 — Translational assessment

Establish:

CQA → exposure → therapeutic relevance

This approach could eventually allow formulation scientists to predict which phytochemicals are most likely to benefit from phospholipid complexation before extensive experimental optimization. [2,7]

21. Conclusion

Phospholipid complexation represents a scientifically relevant strategy for improving the oral pharmaceutical performance of natural compounds with metabolic and antidiabetic potential. The technology is based on association between phytoconstituents and phospholipids, particularly phosphatidylcholine, producing systems with altered physicochemical and membrane-interaction characteristics. [1,2,14]

Evidence from berberine, quercetin and silybin demonstrates that selected phospholipid complexes can substantially improve systemic exposure, including in human pharmacokinetic studies. [8-13] Nevertheless, the field should move beyond the generalized claim that phytosomes "enhance bioavailability." Improved particle size, dissolution or spectroscopic characteristics represent **formulation evidence**, whereas increased C_{max} and AUC represent **pharmacokinetic evidence**. These should not be conflated. [2,8-13]

The major scientific opportunity is therefore to establish a quantitative relationship between:

phytochemical structure → phospholipid interaction → critical quality attributes → stability → absorption → systemic exposure.

Arbutin represents a particularly interesting emerging candidate because its metabolic activity has been documented while its formulation development continues to evolve. A rational arbutin-phospholipid system could therefore serve as a

useful model for investigating how molecular structure determines phospholipid complexation and subsequent bioavailability. [18,2]

Future development of phytosomal systems should incorporate QbD, advanced molecular characterization, standardised raw materials, scalable manufacturing, robust stability testing and pharmacokinetic evaluation. Such an approach would move phytosomes from empirically optimized herbal formulations toward mechanism-based, reproducible and translational pharmaceutical delivery systems. [2,5,7]

Table 3. Proposed critical framework for evaluating a phytosome

Level	Question	Recommended evidence
Molecular	Can the phytochemical interact with phospholipid?	FTIR/NMR/molecular studies
Complexation	Has a genuine complex formed?	Complexation efficiency + DSC/XRD/FTIR
Physical	Is the formulation physically stable?	Size/PDI/zeta potential
Pharmaceutical	Has formulation performance improved?	Dissolution/solubility
Biopharmaceutical	Has absorption improved?	Permeability/PK
Pharmacokinetic	Has systemic	C _{max} /AUC/T _{max} /t _{1/2}

	exposure increased?	
Translational	Is the formulation reproducible?	Scale-up/stability/batch consistency

Source basis: [2,7].

This table is particularly important for the novelty of your review. It changes the manuscript from a conventional "phytosomes are useful" review into a **critical framework for evaluating whether a phytosome has actually solved the bioavailability problem.**

Table 4. Recommended minimum characterization package

Characterization	Purpose	Interpretation
Assay/content	Quantification	Dose consistency
Complexation efficiency	Determine associated phytochemicals	Extent of complex formation
FTIR	Molecular interactions	Supporting evidence
DSC	Thermal behaviour	Physical-state changes
XRD	Crystallinity	Molecular organization
Particle size	Physical characteristics	Dispersion
PDI	Distribution	Uniformity
Zeta potential	Surface properties	Stability indication
SEM/TEM	Morphology	Structural confirmation
Dissolution	Pharmaceutical performance	Release behaviour

Stability	Shelf-life	Product quality
PK	Systemic exposure	Actual bioavailability evidence

Source basis: [2,7].

Proposed graphical abstract

Natural phytochemical

Poor solubility | poor permeability | instability | metabolism

↓

PHOSPHOLIPID COMPLEXATION

Phytochemical + phosphatidylcholine

↓

Molecular interaction

↓

Optimized phytosome

↓

Improved physicochemical properties

↓

Improved dissolution + membrane interaction

↓

Improved oral absorption

↓

↑ Cmax | ↑ AUC | improved systemic exposure

↓

Potential improvement in therapeutic translation

References

1. Lu M, Qiu Q, Luo X, et al. Phospholipid complexes (phytosomes): a novel strategy to improve the bioavailability of active constituents. *Asian J Pharm Sci.* 2019;14(3):265–274.
2. Barani M, Sangiovanni E, Angarano M, et al. Phytosomes as innovative delivery systems for phytochemicals: a comprehensive review of literature. *Int J Nanomedicine.* 2021;16:6983–7022. doi:10.2147/IJN.S318416.
3. Chauhan D, Yadav PK, Sultana N, et al. Advancements in nanotechnology for the delivery of phytochemicals. *J Integr Med.* 2024;22(4):385–398.
4. Bioactive compounds formulated in phytosomes administered as complementary therapy for metabolic disorders. *Int J Mol Sci.* 2024;25:4162.
5. Raghav A, Attri M, Chaudhary H. Review of phytosomes and ethosomes: groundbreaking approaches for delivering the phytochemical components of plants. *Curr Drug Deliv.* 2025;22(6):666–677. doi:10.2174/0115672018282264240218034853.
6. Koppula S, Shaik B, Maddi S. Phytosomes as a new frontier and emerging nanotechnology platform for phytopharmaceuticals: therapeutic and

- clinical applications. *Phytother Res.* 2025. doi:10.1002/ptr.8465.
7. 7. Kumar S, Alsaidan OA, Alzarea SI, et al. Integrating Quality by Design (QbD) in phytosomal drug delivery: a new era in precision phytotherapy. *AAPS PharmSciTech.* 2025;26:198. doi:10.1208/s12249-025-03191-8.
8. 8. Yu F, Li Y, Chen Q, et al. Monodisperse microparticles loaded with self-assembled berberine-phospholipid complex-based phytosomes for improving oral bioavailability and enhancing hypoglycemic efficiency. *Eur J Pharm Biopharm.* 2016;103:136–148. doi:10.1016/j.ejpb.2016.03.019.
9. 9. Riva A, Ronchi M, Petrangolini G, Bosisio S, Allegrini P. Improved oral absorption of quercetin from Quercetin Phytosome®, a new delivery system based on food grade lecithin. *Eur J Drug Metab Pharmacokinet.* 2019;44:169–177. doi:10.1007/s13318-018-0517-3.
10. 10. Barzaghi N, Crema F, Gatti G, Pifferi E, Perucca E. Pharmacokinetic studies on IdB 1016, a silybin-phosphatidylcholine complex, in healthy human subjects. *Eur J Drug Metab Pharmacokinet.* 1990;15(4):333–338. doi:10.1007/BF03190223.
11. 11. Gatti G, Perucca E. Plasma concentrations of free and conjugated silybin after oral intake of a silybin-phosphatidylcholine complex in healthy volunteers. *Int J Clin Pharmacol Ther.* 1994;32(11):614–617.
12. 12. Méndez-Sánchez N, Dibildox-Martinez M, Sosa-Noguera J, et al. Superior silybin bioavailability of silybin-phosphatidylcholine complex in oily-medium soft-gel capsules versus conventional silymarin tablets in healthy volunteers. *BMC Pharmacol Toxicol.* 2019;20:5. doi:10.1186/s40360-018-0280-8.
13. 13. Development of an innovative berberine food-grade formulation with an ameliorated absorption: in vitro evidence confirmed by healthy human volunteers pharmacokinetic study. *Nutrients.* 2021.
14. 14. Phospholipid complex technique for superior bioavailability of phytoconstituents. *Adv Pharm Bull.* 2017;7(1):35–42. doi:10.1517/apb.2017.005.
15. 15. An overview of herbal-based antidiabetic drug delivery systems: focus on lipid- and inorganic-based nanoformulations. *Pharmaceutics.* 2022;14:2135.
16. 16. Oral nano drug delivery systems for the treatment of type 2 diabetes mellitus: an available administration strategy for antidiabetic phytochemicals. 2024.
17. 17. Recent updates on phytopharmaceuticals-based novel phytosomal systems and their clinical trial status: a translational perspective. 2024.
18. 18. Arbutin ameliorates hyperglycemia, dyslipidemia and oxidative stress and modulates adipocytokines and PPAR γ in high-fat diet/streptozotocin-induced diabetic rats. *Life Sci.* 2023;321:121612. doi:10.1016/j.lfs.2023.121612.