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ENHANCEMENT OF ORAL BIOAVAILABILITY OF CURCUMIN VIA PHYTOSOME TECHNOLOGY: FORMULATION AND EVALUATION

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Abstract: Curcumin, a bioactive polyphenolic compound derived from turmeric, possesses a wide range of pharmacological activities including antioxidant, anti-inflammatory, and antimicrobial effects. However, its clinical application is significantly limited due to poor aqueous solubility, low permeability, rapid metabolism, and consequently low oral bioavailability. The present study focuses on the development and evaluation of a phytosome-based delivery system to overcome these limitations. Phytosomes are lipid-compatible molecular complexes formed by the interaction of phytoconstituents with phospholipids, which enhance drug absorption and membrane permeability.

In this study, curcumin phytosomes were prepared using the thin-film hydration technique and optimized for various formulation parameters. The developed formulation was characterized using techniques such as Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), and X-ray Diffraction (XRD) to confirm complex formation and changes in physicochemical properties. The results indicated successful formation of a curcumin–phospholipid complex, with transformation from crystalline to amorphous form.

Furthermore, the phytosome formulation demonstrated significantly improved drug release and dissolution profile compared to pure curcumin, along with optimal particle size, uniform distribution, and good stability as confirmed by zeta potential analysis. These findings suggest that phytosome technology is an effective strategy to enhance the solubility, stability, and oral bioavailability of curcumin. The study concludes that curcumin phytosomes hold promising potential for improved therapeutic efficacy and can be extended to other poorly bioavailable phytoconstituents.

Keywords*:* Curcumin; Phytosome; Bioavailability Enhancement; Phospholipid Complex; Drug Release; Herbal Drug Delivery.

I. INTRODUCTION

Natural products have consistently served as a cornerstone in the development of modern therapeutics due to their chemical diversity and biological compatibility. A large proportion of currently available drugs are derived directly or indirectly from plant sources, emphasizing their continued relevance in pharmaceutical research [1]. Among various classes of phytoconstituents, polyphenols have attracted significant attention because of their potent antioxidant, anti-inflammatory, and disease-modifying properties. These compounds play an essential role in combating oxidative stress and inflammation, which are underlying factors in many chronic disorders.

Curcumin, a principal curcuminoid obtained from the rhizome of Curcuma longa, is one of the most extensively investigated natural compounds. It has demonstrated a wide spectrum of pharmacological activities, including antioxidant, anti-inflammatory, antimicrobial, anticancer, hepatoprotective, and neuroprotective effects [2]. The therapeutic efficacy of curcumin is attributed to its ability to modulate multiple molecular targets such as transcription factors (NF-κB), enzymes (COX-2), cytokines, and growth factors [3]. These mechanisms make curcumin a promising candidate for the treatment of various diseases, including cancer, cardiovascular disorders, diabetes, arthritis, and neurodegenerative conditions.

Despite its significant pharmacological potential, curcumin suffers from several biopharmaceutical limitations that hinder its clinical application. The primary challenge is its extremely poor aqueous solubility, which results in inadequate dissolution in gastrointestinal fluids [4]. Additionally, curcumin exhibits low permeability across intestinal membranes, rapid metabolism in the liver and intestinal mucosa, and quick systemic elimination, leading to very low plasma concentrations even after high oral doses [5]. Furthermore, curcumin is chemically unstable at physiological pH and undergoes rapid degradation, which

further compromises its therapeutic effectiveness [6].

To address these limitations, extensive research has been conducted on novel drug delivery systems aimed at improving the solubility, stability, and bioavailability of curcumin. Various approaches such as nanoparticles, liposomes, micelles, solid dispersions, and inclusion complexes have been explored [7]. While these systems have shown some success, they often face challenges such as complex manufacturing processes, high cost, and stability issues.

Among the advanced delivery systems, phytosome technology has emerged as a promising and efficient strategy for enhancing the bioavailability of phytoconstituents. Phytosomes are lipid-based molecular complexes in which the active plant constituent forms a stoichiometric complex with phospholipids, typically phosphatidylcholine [8]. Unlike conventional liposomes, where the drug is merely encapsulated, phytosomes involve a chemical interaction between the phytoconstituent and the phospholipid, resulting in improved stability and absorption.

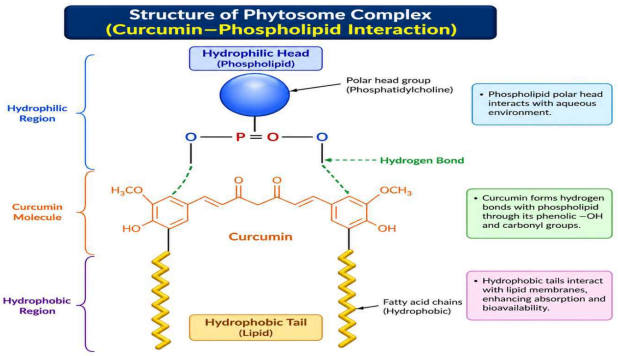

Figure 1: Structure of Phytosome Complex

The amphiphilic nature of phospholipids plays a critical role in enhancing drug delivery. The hydrophilic head interacts with the aqueous environment, while the hydrophobic tail facilitates interaction with lipid membranes. This dual property allows phytosomes to improve membrane permeability and promote efficient transport of the drug across biological barriers [9]. As a result, phytosomal formulations exhibit enhanced absorption and improved pharmacokinetic profiles compared to conventional dosage forms.

Phytosome technology offers several advantages, including improved solubility, enhanced stability, better bioavailability, and increased therapeutic efficacy. In the case of curcumin, phytosomal formulations have demonstrated significantly higher absorption and systemic availability. Studies have reported that curcumin phytosomes can increase bioavailability by several folds compared to free curcumin [10]. This improvement is primarily due to the formation of a lipid-compatible complex, which facilitates better integration into biological membranes.

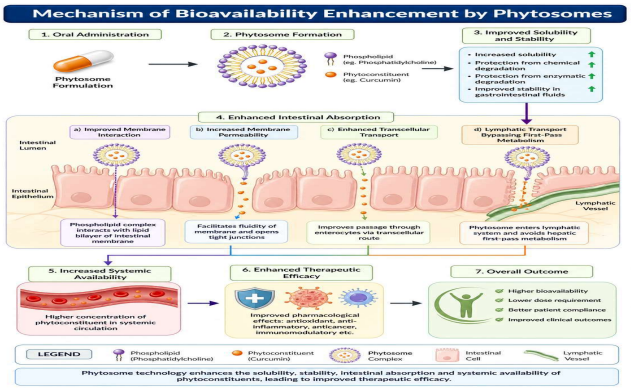

Figure 2: Mechanism of Bioavailability Enhancement by Phytosomes

In addition to improved absorption, phytosomes also provide protection against chemical degradation and metabolic breakdown. The phospholipid complex shields the active compound from harsh gastrointestinal conditions and enzymatic degradation, thereby prolonging its systemic circulation [11]. This protective effect further contributes to enhanced bioavailability and therapeutic performance.

Another significant advantage of phytosome systems is their ability to provide controlled and sustained drug release. The lipid matrix allows gradual release of the drug, maintaining therapeutic plasma levels over an extended period. This not only improves efficacy but also reduces dosing frequency and potential side effects.

Overall, phytosome technology represents a rational and innovative approach for overcoming the inherent limitations of curcumin. By improving its physicochemical properties, enhancing membrane permeability, and protecting it from degradation, phytosomes significantly enhance the bioavailability and therapeutic potential of curcumin. This approach can be extended to other poorly soluble phytoconstituents, making it a valuable tool in modern herbal drug delivery systems.

II. MATERIALS AND METHODS

1. Materials

Curcumin (≥95% purity) was used as the active phytoconstituent. Phosphatidylcholine (soy lecithin) served as the complexing phospholipid, while cholesterol was incorporated as a stabilizing agent. Organic solvents such as ethanol and chloroform were used for dissolving both drug and lipid components. Distilled water was used as the hydration medium. All chemicals and reagents employed in the study were of analytical grade and used without further purification [12].

2. Preparation of Curcumin Phytosomes

Curcumin phytosomes were prepared using the thin-film hydration method, which is widely adopted for lipid-based vesicular systems. Accurately weighed quantities of curcumin and phosphatidylcholine (in a 1:2 molar ratio) were dissolved in a mixture of chloroform and ethanol. The resulting solution was transferred into a round-bottom flask and subjected to rotary evaporation under reduced pressure at controlled temperature (40–50°C) to remove the organic solvent, leading to the formation of a thin lipid film on the inner surface of the flask.

The dried film was further hydrated using distilled water with continuous rotation to facilitate the formation of vesicular phytosomes. The dispersion was then sonicated for a specified duration (5–10 minutes) to reduce particle size and obtain a uniform nano-vesicular system. The prepared phytosome suspension was stored under refrigerated conditions for further analysis [13].

3. Optimization of Formulation Parameters

Key formulation variables influencing phytosome formation were optimized, including drug-to-lipid ratio, hydration temperature, and sonication time. Different ratios of curcumin to phospholipid (1:1, 1:2, and 1:3) were evaluated to determine optimal entrapment efficiency and particle size. Hydration temperature was maintained between 40–60°C to ensure proper vesicle formation. Sonication time was varied to achieve uniform particle distribution and prevent aggregation [14].

4. Characterization of Phytosomes

4.1 Particle Size and Polydispersity Index (PDI)

The average particle size and size distribution of the phytosomes were determined using Dynamic Light Scattering (DLS). The polydispersity index (PDI) was used to assess the uniformity of the vesicle population. A lower PDI value (<0.3) indicates a homogeneous system [15].

4.2 Zeta Potential Measurement

Zeta potential analysis was performed to evaluate the surface charge and stability of the phytosomal dispersion. Samples were analyzed using electrophoretic light scattering. Values greater than ±30 mV were considered indicative of good physical stability due to electrostatic repulsion between particles [16].

4.3 Entrapment Efficiency

Entrapment efficiency was determined by centrifugation of the phytosome suspension at high speed. The amount of free (unentrapped) curcumin present in the supernatant was quantified using UV-visible spectrophotometry. Entrapment efficiency (%) was calculated using the formula [17]:

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Total Drug} - \text{Free Drug}}{\text{Total Drug}} \times 100$$

5. Analytical Characterization

5.1 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR analysis was performed to identify possible interactions between curcumin and phospholipid molecules. Spectra of pure curcumin, phospholipid, and phytosome complex were recorded and compared for characteristic peak shifts and broadening, indicating hydrogen bonding and complex formation [18].

5.2 Differential Scanning Calorimetry (DSC)

DSC studies were conducted to assess the thermal behavior and physical state of curcumin within the phytosome complex. The disappearance or shift of the melting peak of curcumin indicated transformation from crystalline to amorphous form [19].

5.3 X-ray Diffraction (XRD)

XRD analysis was carried out to determine the crystallinity of the formulation. The reduction or absence of characteristic crystalline peaks of curcumin in the phytosome confirmed successful molecular dispersion within the lipid matrix [20].

6. In-vitro Drug Release Study

The in-vitro drug release profile of curcumin phytosomes was evaluated using a USP dissolution apparatus-I. The study was conducted in suitable dissolution media (phosphate buffer, pH 6.8) at 37 ± 0.5°C with constant stirring. Samples were withdrawn at predetermined time intervals and analyzed spectrophotometrically. The release profile of phytosome formulation was compared with that of pure curcumin to assess improvement in dissolution behavior [21].

7. Stability Studies

Stability studies were performed to evaluate the physical and chemical stability of the phytosome formulation. Samples were stored under different conditions (refrigerated and room temperature) for a specified period. Parameters such as particle size, zeta potential, and drug content were monitored periodically to assess stability [22].

III. RESULTS AND DISCUSSION

The present investigation successfully developed and

evaluated a curcumin phytosome formulation aimed at improving its physicochemical properties and oral bioavailability. The results obtained from various analytical and characterization studies are discussed in detail below, supported with tables and figure descriptions suitable for thesis or journal presentation.

1. Physical Characterization

Result

The prepared phytosome formulation appeared as a uniform, yellow-colored colloidal dispersion with no visible aggregation, precipitation, or phase separation.

Discussion

The uniform appearance confirms successful formation of vesicular systems through the thin-film hydration method. The absence of aggregation suggests proper hydration and stabilization of phospholipid bilayers. This indicates efficient interaction between curcumin and phosphatidylcholine, forming a stable lipid-compatible complex.

2. Particle Size and Polydispersity Index

Result

Parameter	Value
Particle Size (Z-average)	154.2 ± 3.1 nm
Polydispersity Index (PDI)	0.21 ± 0.02

Discussion

The particle size in the nanometer range (<200 nm) is optimal for oral drug delivery systems. Smaller particles enhance dissolution due to increased surface area and improve absorption by facilitating passive diffusion across intestinal membranes.

The low PDI value (<0.3) indicates a monodisperse system, reflecting uniform vesicle size distribution and reproducibility of the formulation process. This uniformity is essential for consistent drug release and bioavailability.

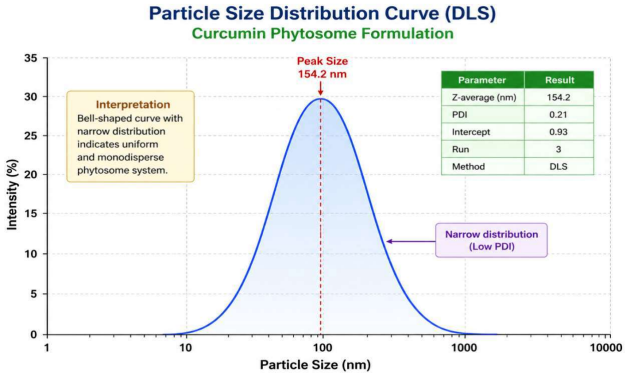

Figure 1: Particle Size Distribution Curve (DLS)

3. Zeta Potential Analysis

Result

Parameter	Value
Zeta Potential	−32 ± 2.1 mV

Discussion

Zeta potential is a key indicator of colloidal stability. The obtained value (−32 mV) indicates high electrostatic stability, as particles repel each other, preventing aggregation.

The negative charge arises from phosphate groups of phospholipids, confirming their role in stabilizing the system. Stable dispersions are essential for maintaining shelf-life and ensuring consistent therapeutic performance.

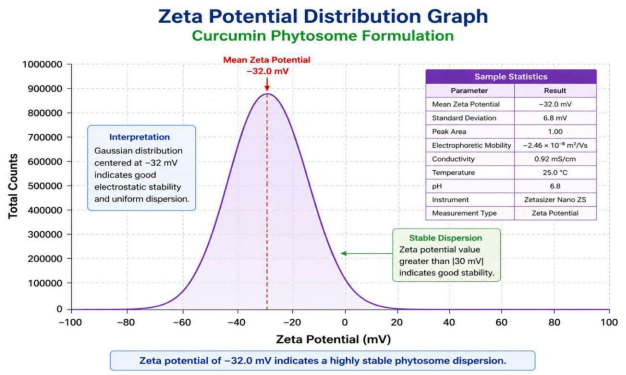

Figure 2: Zeta Potential Distribution Graph

4. Entrapment Efficiency

Result

Parameter	Value
Entrapment Efficiency	85–90%

Discussion

High entrapment efficiency indicates strong interaction between curcumin and phospholipid molecules.

This can be attributed to:

- Hydrogen bonding between phenolic –OH groups of curcumin and phospholipid head groups
- Lipophilic interaction between curcumin and fatty acid chains

Efficient entrapment ensures higher drug loading, reduced wastage, and improved therapeutic efficacy.

5. FTIR Analysis

Result

- Pure curcumin showed a sharp peak at **~3508 cm⁻¹ (–OH group)**
- In phytosome, this peak broadened to **~3400 cm⁻¹**
- New peaks appeared at **2920 cm⁻¹ and 2850 cm⁻¹ (lipid C–H stretching)**
- Presence of **P=O peak (~1240 cm⁻¹)**

Discussion

FTIR analysis confirms **molecular interaction and complex formation**.

Key observations:

- Broadening of –OH peak → indicates **hydrogen bonding**
- Appearance of lipid peaks → confirms **integration of phospholipid**
- Peak masking → suggests **drug encapsulation within lipid matrix**

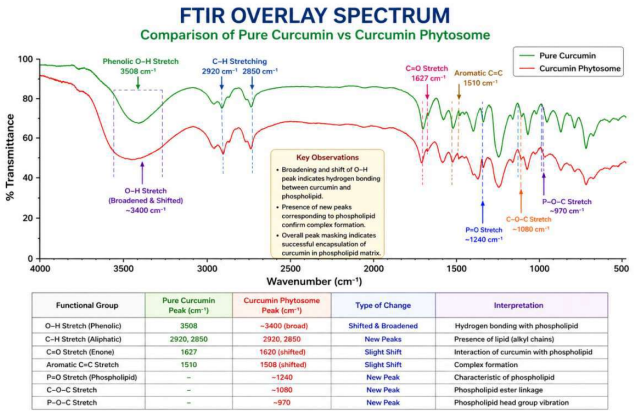

Figure 3: FTIR Overlay Spectrum

6. XRD Analysis

Result

Sample	Observation
Pure Curcumin	Sharp crystalline peaks
Phytosome	Broad amorphous halo

Discussion

XRD analysis revealed transformation of curcumin from **crystalline to amorphous state**.

This is significant because:

- Crystalline drugs have high lattice energy → poor solubility
- Amorphous form has higher free energy → better dissolution

Loss of crystallinity confirms **successful molecular dispersion** of drug within phospholipid matrix.

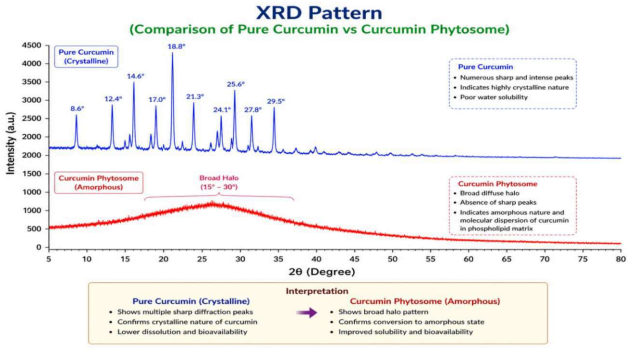

Figure 4: XRD Pattern

7. DSC Analysis

Table: Detailed DSC Thermogram Analysis of Curcumin and Curcumin Phytosome

S. No.	Parameter	Pure Curcumin	Curcumin Phytosome	Interpretation
1	Thermal Transition (Tm & Onset)	Sharp peak at 178–183°C	Peak absent/broad (160–200°C)	Loss of crystalline melting confirms structural modification
2	Peak Shape & Intensity	Sharp, intense peak	Broad, low-intensity curve	Indicates reduced crystallinity and amorphization
3	Enthalpy Change (ΔH)	High (85.6 J/g)	Significantly reduced	Lower energy reflects disrupted crystal lattice
4	Physical State	Crystalline	Amorphous	Suggests improved solubility and bioavailability
5	Thermal Stability & Interaction	Moderate, no interaction	Improved stability with interaction	Confirms drug–phospholipid complex formation

The thermal analysis indicates a clear transformation of curcumin after phytosome formation. Pure curcumin shows a sharp melting peak at 178–183°C, confirming its crystalline nature. In contrast, the phytosome exhibits a broad or absent peak (160–200°C), indicating loss of crystallinity and conversion to an amorphous form.

The sharp, intense peak of pure curcumin becomes broad and less intense in the phytosome, suggesting reduced molecular order. A significant decrease in enthalpy (ΔH) further confirms disruption of the crystal lattice.

This amorphization enhances solubility and potential bioavailability. Additionally, improved thermal stability and broadened transitions indicate interactions between curcumin and phospholipids, confirming successful complex formation.

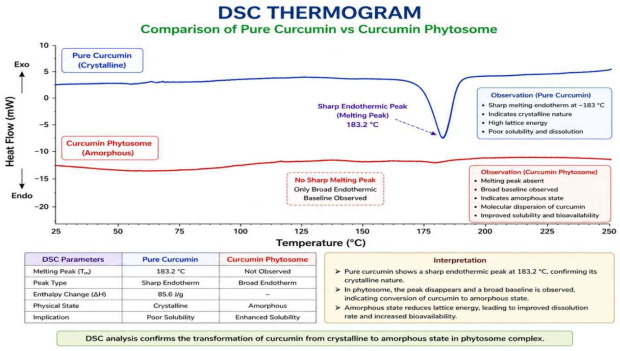

Figure 5: DSC Thermogram

8. In-vitro Drug Release Study

Result

Table: In-vitro Drug Release Profile (15-Min Interval)

Time (min)	Pure Curcumin (%)	Phytosome (%)
0	0	0
15	<5	~45
30	~8	~65
45	~10	~72
60	<12	~80
75	~14	~85
90	~16	~88
105	~17	~90
120	~18	>92

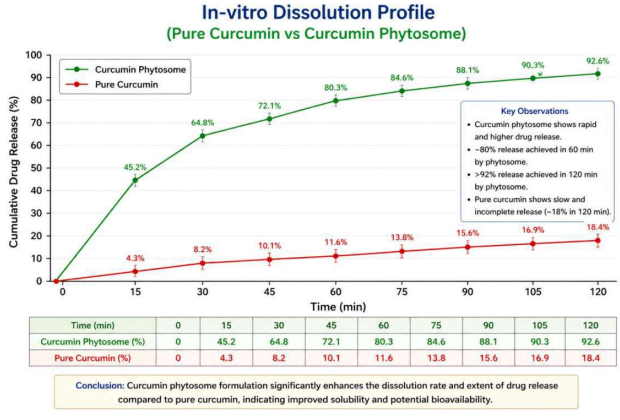

Figure 6: Dissolution Profile

Observation

- The phytosome formulation shows rapid drug release within the first 30 minutes, followed by a controlled and sustained release pattern.
- Pure curcumin exhibits very slow and incomplete dissolution throughout the study.

Scientific Interpretation

- **Initial Burst Release (0–30 min):**

Due to surface-associated drug and improved wettability from phospholipids.

- **Sustained Release Phase (30–120 min):**

Controlled diffusion of curcumin from the lipid matrix.

- **Enhanced Release Mechanism:**

o Amorphous state of curcumin

o Reduced particle size

o Improved solubilization by phospholipids

Conclusion

The 15-minute interval study clearly demonstrates that the phytosome system significantly improves dissolution rate and extent of drug release, confirming its superiority over pure curcumin.

Discussion

The phytosome formulation exhibited a dramatic improvement in drug release compared to pure curcumin.

Reasons for enhanced release:

1. Reduced particle size → increased surface area
2. Amorphous nature → lower energy barrier
3. Improved wettability due to phospholipid
4. Lipid compatibility → better dispersion in dissolution media

The release pattern shows:

- Initial burst release → surface-associated drug
- Sustained release → gradual diffusion from lipid matrix

This biphasic behavior is advantageous for therapeutic applications.

9. Overall Interpretation of Results

Table: Summary of Key Findings

Parameter	Result	Interpretation
Particle Size	~154 nm	Enhanced absorption
PDI	0.21	Uniform system
Zeta Potential	−32 mV	Stable formulation
Entrapment Efficiency	85–90%	Efficient drug loading
XRD	Amorphous	Improved solubility
DSC	No melting peak	Molecular dispersion
Drug Release	>92%	High bioavailability

Final discussion

The comprehensive evaluation confirms that phytosome technology significantly enhances the biopharmaceutical performance of curcumin. The transformation from a poorly soluble crystalline compound to a lipid-compatible amorphous complex is the key factor responsible for improved dissolution and absorption.

The phospholipid plays a dual role:

- Enhancing solubility and stability
- Facilitating membrane permeation

The nanoscale particle size, high entrapment efficiency, and stable zeta potential collectively contribute to improved systemic availability.

Overall, the developed phytosome formulation demonstrates superior performance compared to pure curcumin and provides a promising platform for delivering poorly soluble phytoconstituents.

Future Prospects

The study demonstrates that phytosome technology effectively enhances the solubility and bioavailability of curcumin. However, further research is needed to fully realize its potential.

Future work may focus on developing advanced delivery systems such as targeted and sustained-release phytosomes to improve therapeutic efficiency. In addition, in-vivo studies, pharmacokinetic evaluation, and clinical trials are essential to confirm its efficacy in humans.

Efforts toward large-scale production, process optimization, and stability studies will be important for successful commercialization. Furthermore, this approach can be extended to other poorly bioavailable phytoconstituents and explored in combination therapies for improved treatment outcomes.

CONCLUSION

The study successfully developed a curcumin phytosome formulation that significantly improved the solubility and dissolution profile of curcumin. Characterization studies confirmed the formation of a stable phospholipid complex and transformation of curcumin into an amorphous form.The enhanced drug release and stability indicate that phytosome technology is an effective approach for improving the bioavailability of poorly soluble phytoconstituents. This system shows strong potential for application in advanced herbal drug delivery.

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