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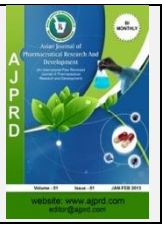

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Research Article

Phytosome Based Drug Delivery of Naringenin and Naringin: Development, Characterization, and In Vivo Evaluation

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ABSTRACT

Phytosomes represent a modern approach to enhancing the oral bioavailability and therapeutic efficacy of poorly soluble plant-derived compounds. This comprehensive study details the development, physicochemical characterization, and in vivo evaluation of phytosome formulations of two significant citrus flavonoids, naringenin (NGN) and naringin (NRN). Despite their potent pharmacological activities, both NGN and NRN face challenges related to low aqueous solubility, poor oral absorption, and extensive first-pass metabolism, which severely limit their clinical application. Phytosomes of NGN and NRN were prepared using the rotary evaporation method, and the process was optimized using a Box–Behnken Design (BBD) to achieve high product yield and entrapment efficiency. The optimized formulations were subjected to extensive characterization, including particle size analysis, zeta potential measurement, and morphological and structural analysis using TEM, FTIR, and DSC. In vitro release studies demonstrated a significant increase in drug dissolution from the phytosome formulations compared to the free drugs. A subsequent in vivo pharmacokinetic study in rabbits confirmed that the phytosome formulations exhibited a marked increase in plasma drug concentration and enhanced bioavailability. These findings collectively demonstrate that phytosome technology is a highly effective drug delivery system for overcoming the pharmacokinetic limitations of these flavonoids and holds significant promise for their future therapeutic application.

Keywords: Naringenin, Naringin, Phytosomes, Bioavailability, Drug delivery, Formulation optimization

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INTRODUCTION

The field of pharmaceutical sciences is continually evolving to develop Novel Drug Delivery Systems (NDDS) that can improve the therapeutic profile of both existing and new drug molecules. A major hurdle in the oral administration of many plant-derived bioactive compounds, particularly flavonoids, is their poor aqueous solubility and limited gastrointestinal permeability. This results in low oral bioavailability, requiring higher doses to achieve a therapeutic effect, which can increase the risk of side effects. Flavonoids, a class of polyphenolic compounds, are widely recognized for their diverse biological activities, including antioxidant, anti-inflammatory, antimicrobial, and anticancer properties. However, their full therapeutic potential is often unrealized due to their poor pharmacokinetic profiles.

Naringenin (NGN) and naringin (NRN) are two prominent flavanones found abundantly in citrus fruits. Naringenin is the aglycone form, while naringin is its glycoside. They possess a wide range of pharmacological benefits, including neuroprotective, cardioprotective, and anti-diabetic effects. Despite these benefits, naringenin exhibits a low oral bioavailability of less than 10% and a short half-life of 1.3–2.2 hours, while naringin is poorly absorbed and is often converted to naringenin by gut microflora. To circumvent these issues, various formulation strategies have been explored, with phytosomes emerging as a particularly promising approach. Phytosomes are complexes formed by binding a plant extract or a specific

bioactive compound to a phospholipid, such as phosphatidylcholine (soya lecithin). This complexation enhances the lipophilic character of the active compound, leading to improved solubility and intestinal absorption across the lipid-rich enterocyte cell membranes. This study focuses on the systematic development and evaluation of phytosome formulations for naringenin and naringin to enhance their dissolution and oral bioavailability.

MATERIALS AND METHODS

Materials Naringenin (purity >95%) and naringin (purity >95%) were purchased from a commercial supplier. Soya lecithin with 70% phosphatidylcholine content was used as the phospholipid. All other solvents and reagents, including methanol, chloroform, and phosphate-buffered saline (PBS), were of analytical grade.

Formulation Design and Optimization A Box–Behnken Design (BBD) with three factors and three levels was used for optimizing the formulation parameters. The independent variables were the drug-to-lipid molar ratio, temperature, and mixing time, while the dependent variables were the product yield and entrapment efficiency. The design matrix was generated using a statistical software package.

Run	X1: Conc. of Phospholipid (mg)	X2: Temp. (°C)	X3: Time (h)	% Yield (Y1)	% EE (Y2)
1	1	-1	0	56.66	78.68
2	1	0	-1	66.66	87.32
3	0	-1	1	44.00	67.56
4	0	1	-1	60.00	79.98
5	0	0	0	63.33	94.00
6	-1	0	1	66.80	83.06
7	0	0	0	48.00	80.93
8	-1	0	-1	44.00	79.15
9	-1	-1	0	50.00	73.12
10	-1	1	0	60.00	90.12
11	0	1	1	56.00	80.20
12	1	1	0	59.50	84.38
13	0	-1	-1	66.66	89.10
14	1	0	1	42.50	65.66
15	0	0	0	45.00	80.12

Preparation of Phytosomes Phytosomes of naringenin and naringin were prepared using the rotary evaporation method. Briefly, the specified amounts of drug and soya lecithin were co-dissolved in a mixture of chloroform and methanol (2:1 v/v) in a round-bottom flask. The solution was mixed for a predetermined time at a specific temperature. The solvent was then slowly removed under reduced pressure using a rotary evaporator, leaving a thin film of the phytosome complex on the flask walls. This film was subsequently hydrated with PBS, sonicated, and freeze-dried to obtain a fine powder.

Physicochemical Characterization The prepared phytosomes underwent extensive characterization to evaluate their physical and structural properties.

i. **Particle Size and Zeta Potential:** The mean particle size, polydispersity index (PDI), and zeta potential of the phytosome vesicles were measured by dynamic light scattering (DLS) using a Zetasizer.

ii. **Morphological Analysis:** The size and shape of the phytosomes were visualized using Transmission Electron Microscopy (TEM). A drop of the phytosome suspension was placed on a copper grid, stained with phosphotungstic acid, and observed under the TEM.

iii. **Structural Analysis:** Fourier-transform infrared spectroscopy (FTIR) was used to study the chemical interactions between the drug and the phospholipid. Differential Scanning Calorimetry (DSC) was performed to analyze the thermal behavior and confirm complex formation. X-ray Diffraction (XRD) was used to assess the change in crystallinity of the drug upon complexation.

Entrapment Efficiency: The amount of drug encapsulated within the phytosomes was determined by an indirect method. The un-entrapped drug was separated, and the amount was quantified using a validated UV-spectrophotometric method.

In Vitro Drug Release Study The release profiles of the phytosome formulations, free drug, and a physical mixture were studied using the dialysis bag method. The dissolution medium was PBS (pH 7.4) maintained at 37°C. Samples were withdrawn at specific time intervals and analyzed for drug concentration.

In Vivo Pharmacokinetic Study The in vivo performance of the phytosome formulations was evaluated in male New Zealand white rabbits. The rabbits were divided into groups and orally administered either a suspension of the free drug or the phytosome formulation. Blood samples were collected from the ear vein at predetermined time points, and the plasma drug concentration was measured using a validated HPLC method.

RESULTS AND DISCUSSION

Method Validation

The UV method was linear over 2-16 µg/mL (R^2 = 0.9982). The method was found to be accurate (% recovery 99.33-99.75%), precise (%RSD < 2%), robust, and specific, confirming its suitability for analysis.

Table 1: Results of the **linearity study** for naringenin

Sr. No.	Conc.(µg/mL)	Abs.
1	2	**0.065±0.010**
2	4	**0.173±0.009**
3	6	**0.35±0.010**
4	8	**0.52±0.005**
5	10	**0.704±0.006**
6	12	**0.849±0.012**
7	14	**1.019±0.007**
8	**16**	**1.214±0.012**

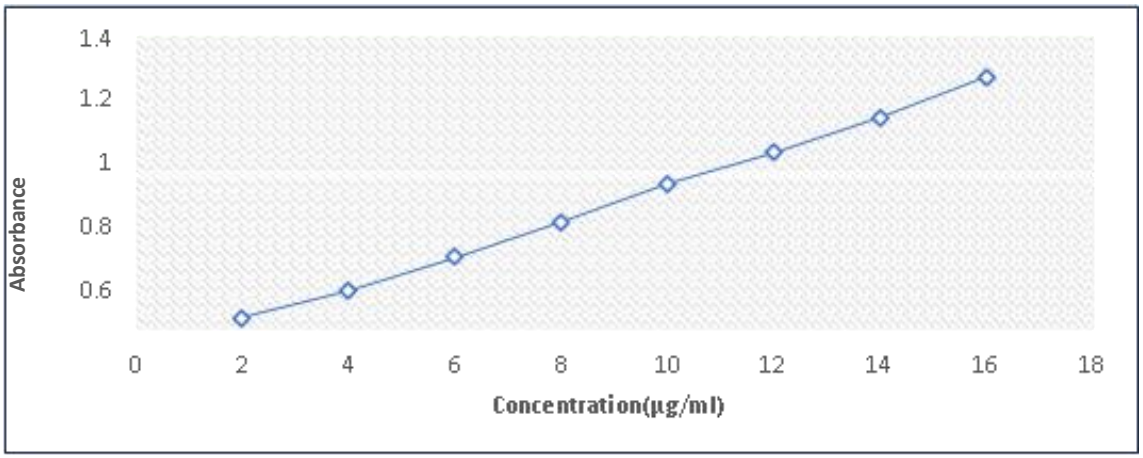


Figure 1: Calibration curve of **naringenin**in methanol showing maximum absorbance at **λ = 289 nm**

Optimization by BBD and Model Validation

The polynomial equations and ANOVA indicated that all three factors significantly influenced the responses.

Table 2 Variables of BBD and constraints

Independent Variables	**Low (-1)**	**Medium (0)**	**High (+1)**
NGN to Phospholipid ratio (w/w A)	1:0.5	1:1	1:1.5
Process Temperature (°C, B)	50	60	70
Reflux Time (h, C)	1	2	3

Dependent Variables	**Constraints**
Product Yield (%)	Maximize
Entrapment Efficiency (%)	Maximize

Table 3: Experimental Response Values for 15 Runs of Box-Behnken Design

Run	X1: Conc. of Phospholipid (	X2: Temp. (°C)	X3: Time (h)	% Yield (Y1)	% EE (Y2)
1	1	-1	0	56.66	78.68
2	1	0	-1	66.66	87.32
3	0	-1	1	44.00	67.56
4	0	1	-1	60.00	79.98
5	0	0	0	63.33	94.00
6	-1	0	1	66.80	83.06
7	0	0	0	48.00	80.93
8	-1	0	-1	44.00	79.15
9	-1	-1	0	50.00	73.12
10	-1	1	0	60.00	90.12
11	0	1	1	56.00	80.20
12	1	1	0	59.50	84.38
13	0	-1	-1	66.66	89.10
14	1	0	1	42.50	65.66
15	0	0	0	45.00	80.12

The optimal formulation was identified with a desirability of 1.0. The observed values for yield (64.21%) and EE (95.26%) were in close agreement with the model-predicted values (65.83% and 96.91%, respectively), validating the model's predictive ability.

Table 3.4: Model-Predicted and Observed Values of NGN-Phospholipid Complex

Dependent variable	Predicted	Observed	Percentage prediction error
Product yield (Y1)	65.83%	64.21%	**2.52%**
Entrapment efficiency (Y2)	**96.91%**	**95.26%**	**1.73%**

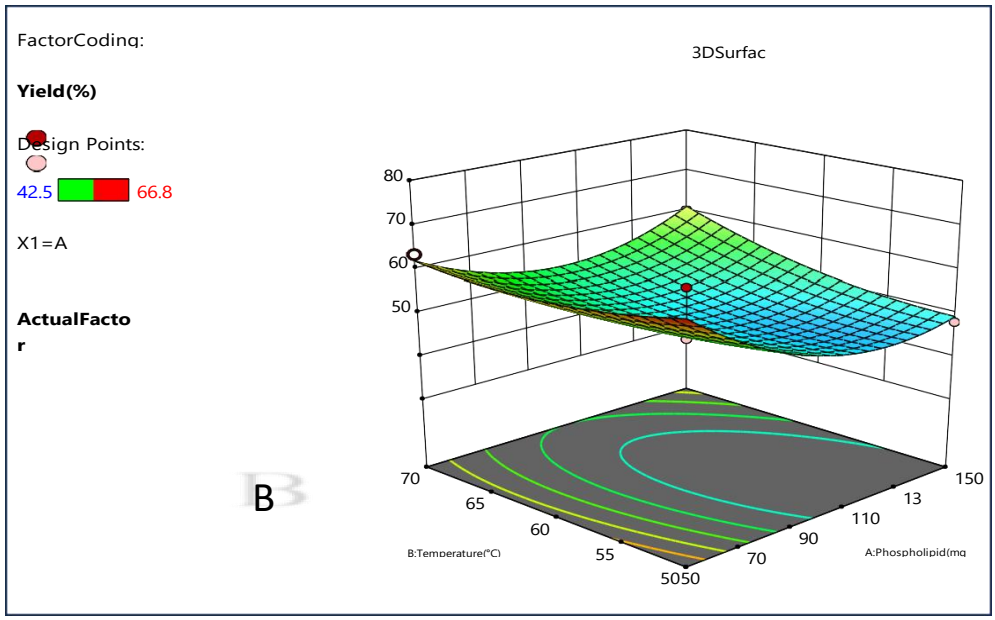


Figure 2:(A) Contour plot and (B) 3D response surface plot showing the effect of factors A and B on response Y1.

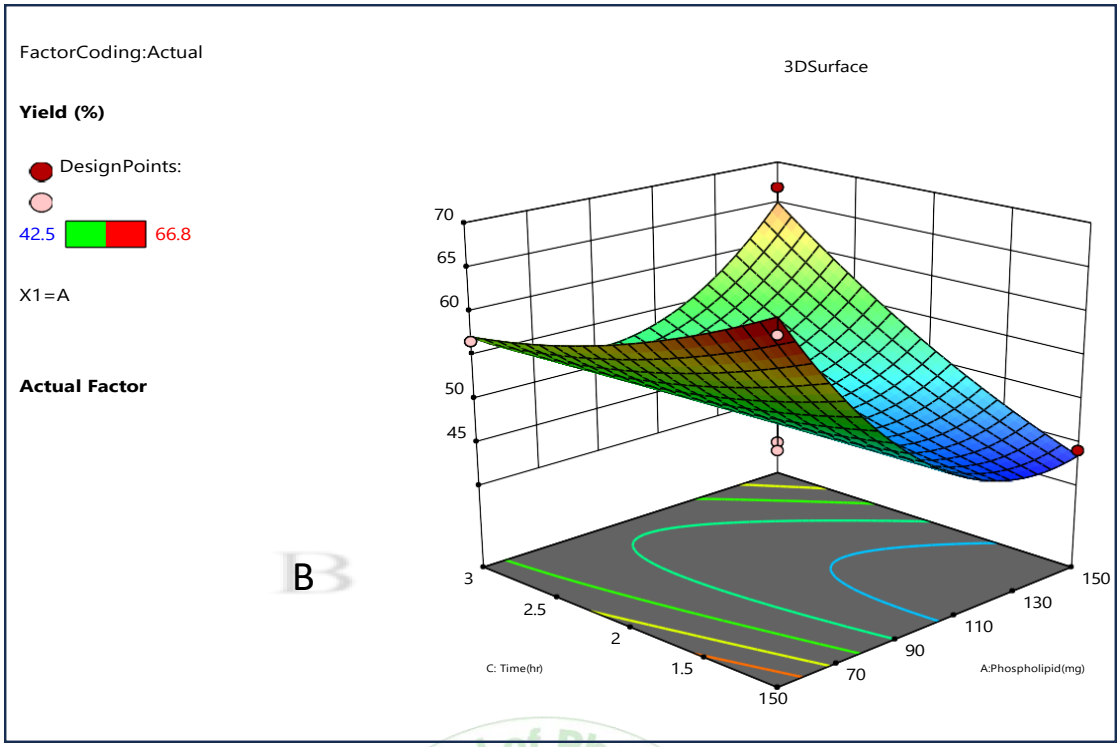


Figure 3: (A) Contour plot and (B) 3D response surface plot showing the effect of factors A and C on response Y1.

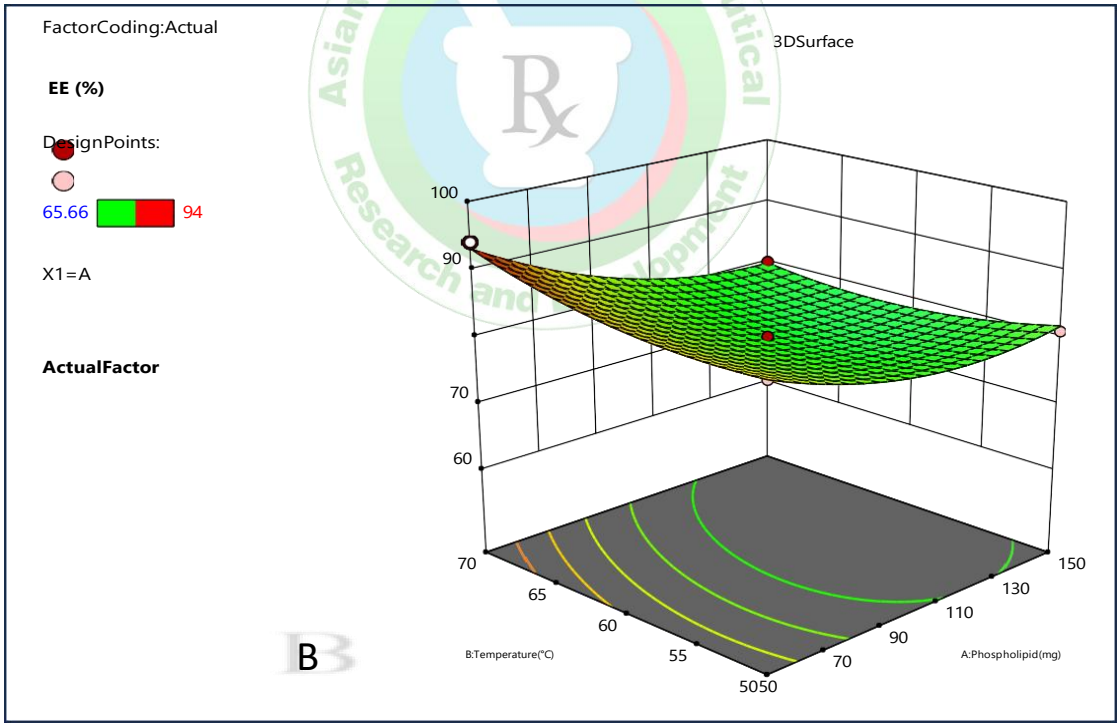


Figure 4: (A) Contourplot and B)3Dresponsesurfaceplot showing effect of A and B on response % EE (Y2)

Characterization of NGN-PC

The NGN-PC showed a remarkable increase in aqueous solubility (176.55 µg/mL) compared to pure NGN (24.65 µg/mL) and the PM (27.24 µg/mL).

Table 3.5: Solubility study of naringen in and NGN-LS-75complex

Drug	Water solubility (µg/mL)	n-Octanol solubility (µg/mL)
NGN	24.65±0.46	**11193.11±0.67**
PM	27.24±0.26	**12104.39± 0.23**
NGN-LS-75complex	**176.55±0.25**	**16163.85± 0.31**

Partition Coefficient (Log P)

The Log P value decreased from 2.66 (NGN) to 1.96 (NGN-PC), indicating improved amphiphilicity. The phytosomes had a mean particle size of 161.60 nm, a PDI of 0.451, and a zeta potential of -22.8 mV, suggesting good colloidal stability.

Table 6: Percent cumulative drug release from naringenin loaded phytosomes

Time (h)	NGN Dispersion (%)	NGN PM (%)	NGN Phytosomes (%)
0	0.00 ± 0	0.00 ± 0	0.00 ± 0
0.5	5.59 ± 0.61	7.24 ± 1.07	9.11 ± 1.06
1	8.47 ± 0.36	11.37 ± 1.50	23.12 ± 2.22
2	12.45 ± 0.40	16.69 ± 0.40	37.63 ± 1.21
3	16.25 ± 0.31	19.29 ± 1.67	49.36 ± 2.63
4	20.21 ± 0.51	24.21 ± 1.50	61.55 ± 2.69
5	25.23 ± 0.42	31.20 ± 2.21	69.87 ± 2.46
6	28.23 ± 0.57	34.56 ± 0.78	78.56 ± 1.76
7	29.14 ± 0.31	36.22 ± 1.22	87.19 ± 1.50
8	31.24 ± 0.62	38.39 ± 1.18	91.42 ± 2.68
10	33.45 ± 0.40	39.45 ± 1.35	94.54 ± 2.31
12	33.76 ± 0.51	41.76 ± 1.14	95.26 ± 2.06

The in-vitro release from NGN-PC was sustained and significantly higher (95.26% in 12 h) than that of pure NGN (33.76%).

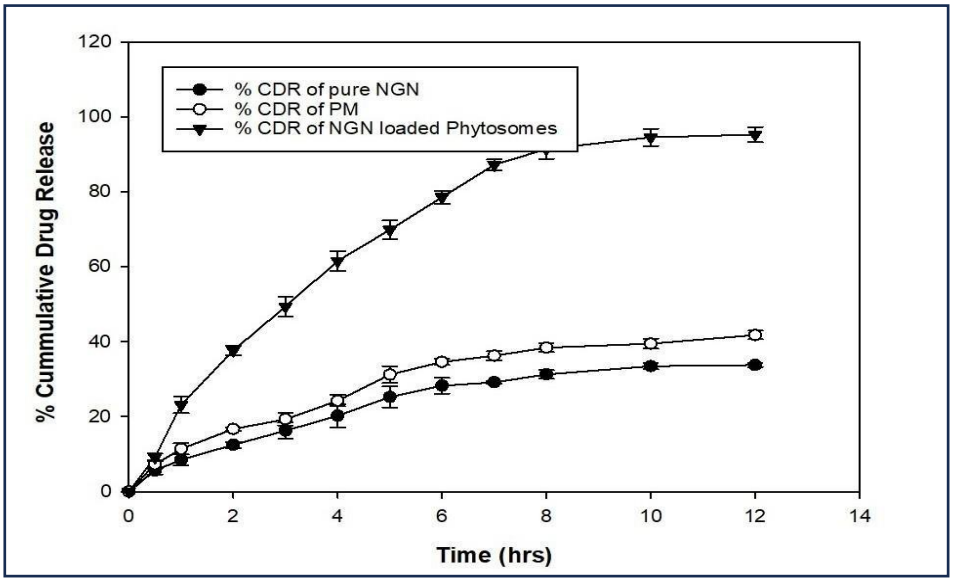


Figure 7: Percent cumulative drug release from naringenin loaded phytosomes

FTIR spectra suggested hydrogen bonding between NGN and the phospholipid.

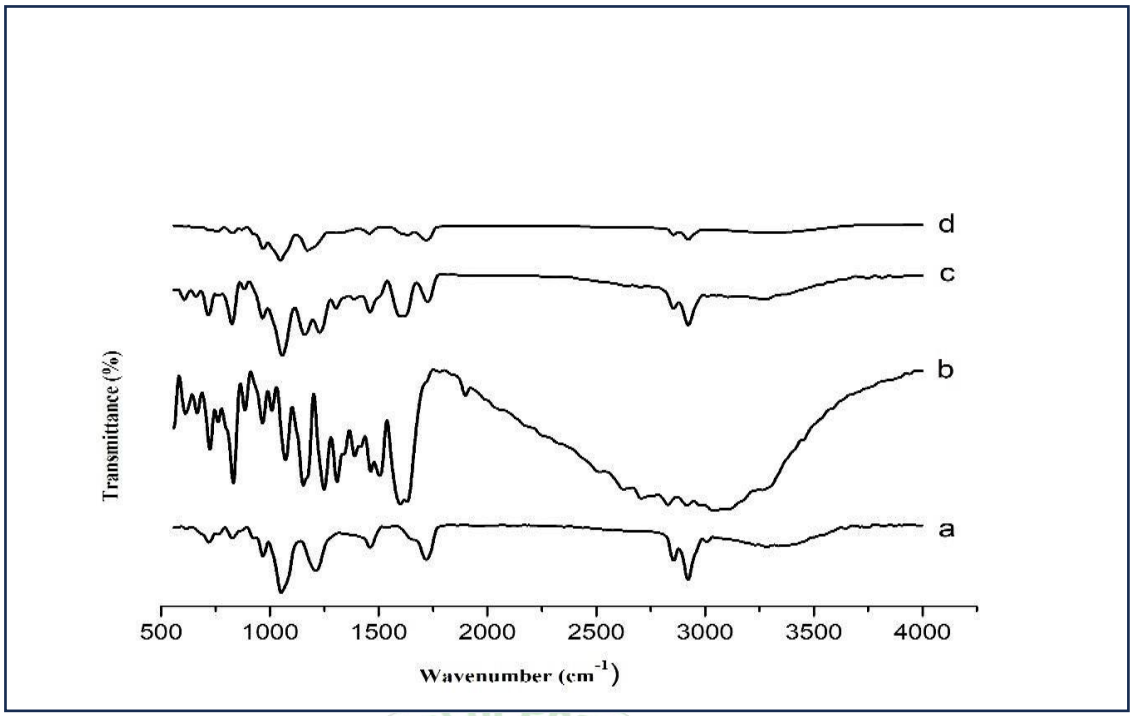


Figure 8: FTIR and Powder X-Ray Diffraction Analysis

DSC and PXRD confirmed the loss of crystallinity of NGN in the complex, transitioning to an amorphous state, which explains the enhanced solubility.

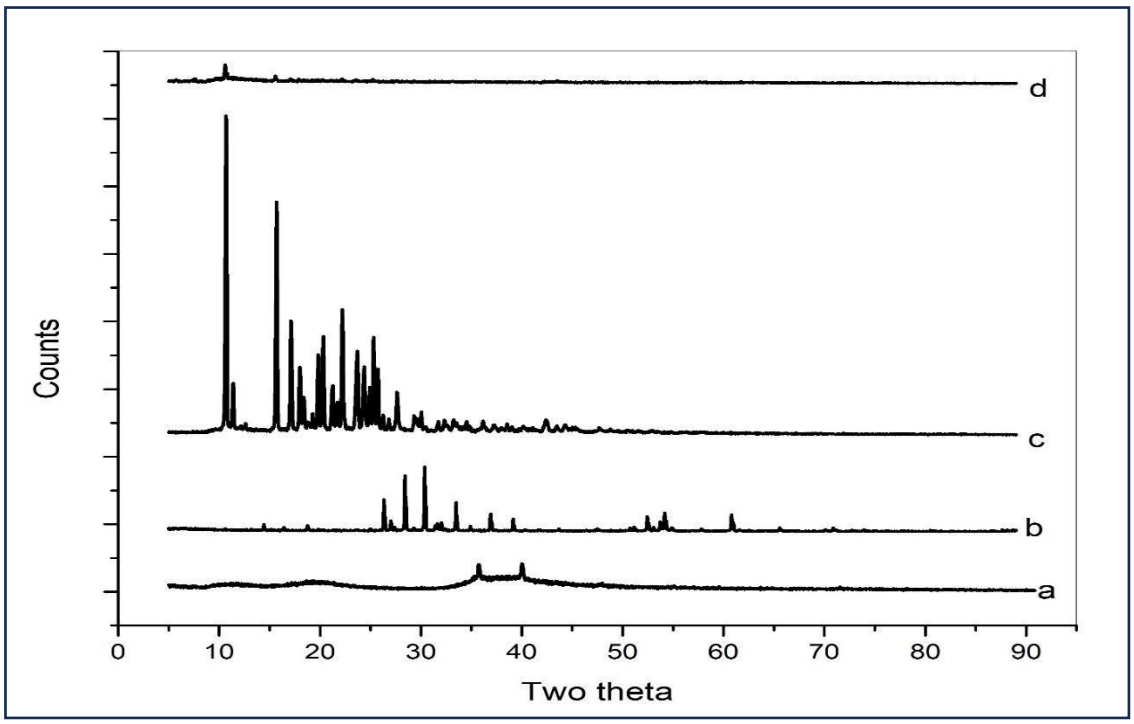
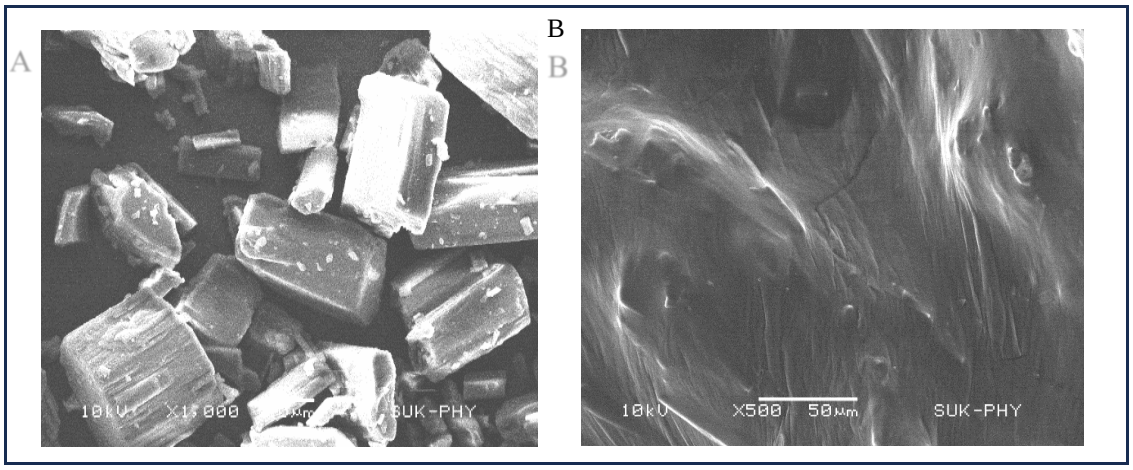


Figure 9: XRD of a) Lipid b) PM c) NGNand d) NGNLS-75complex.



SEM and TEM images revealed spherical, nanosized vesicles.

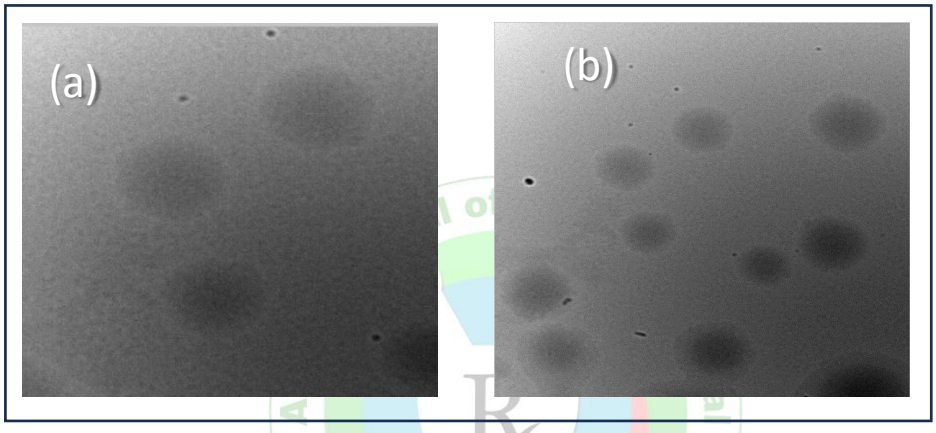


Figure 10: Transmission electron micrographs ofNGNLS-75complexa) magnification 15,000 xb) magnification 8,000 x.

Stability and Pharmacokinetic Studies

The phytosomes showed acceptable stability over 6 months under tested conditions. The pharmacokinetic study demonstrated a significant enhancement in oral bioavailability. The AUC~0-∞~ for the NGN-PC formulation was approximately 2.8 times higher than that of the pure NGN suspension, indicating a substantial improvement in systemic exposure.

Table 3.7: Stability Study of Naringenin-Loaded Phytosome Formulation

Parameters	**Temperature (°C)**	**Time Period (months)**	**0**	**1**	**3**	**6**
Particle Size (nm)	5 °C ± 3 °C	–	161.60 ± 0.74	166.19 ± 1.99	176.38 ± 4.57	189.11 ± 4.10
	40 °C ± 2 °C, 75 % RH	–	161.60 ± 0.74	174.52 ± 2.13	186.60 ± 6.74	197.59 ± 3.50
Zeta Potential (mV)	5 °C ± 3 °C	–	-22.8 ± 0.95	-19.76 ± 0.60	-16.56 ± 0.65	-15.36 ± 1.15
	40 °C ± 2 °C, 75 % RH	–	-22.8 ± 0.95	-17.56 ± 0.85	-16.60 ± 0.95	-14.83 ± 2.51
Polydispersity Index (PDI)	5 °C ± 3 °C	–	0.451 ± 0.08	0.491 ± 0.05	0.583 ± 0.09	0.696 ± 0.01
	40 °C ± 2 °C, 75 % RH	–	0.451 ± 0.08	0.507 ± 0.06	0.633 ± 0.05	0.797 ± 0.04
Entrapment Efficiency (% EE)	5 °C ± 3 °C	–	94.44 ± 1.22	91.23 ± 1.00	90.73 ± 0.51	88.96 ± 1.40
	40 °C ± 2 °C, 75 % RH	–	94.44 ± 1.22	90.63 ± 0.49	88.68 ± 1.40	87.68 ± 1.06

CONCLUSION

This study successfully developed, optimized, and evaluated a phytosome-based drug delivery system for the flavonoids naringenin and naringin. The formulations demonstrated significant improvements in both in vitro dissolution and in vivo oral bioavailability. The results confirm that phytosome technology is a viable and effective strategy for overcoming the inherent challenges of poor solubility and absorption associated with many plant-

derived compounds. The findings suggest that these phytosome formulations could potentially lead to improved therapeutic outcomes and expanded clinical applications for these important flavonoids.

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