ORIGINAL ARTICLE

Development and Characterization of a Novel Dual Phytosome Loaded with Resveratrol and Syringic Acid for Parkinson's Therapy

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Abstract

Aim: The present study aimed to develop and evaluate phytosomal formulations of resveratrol, syringic acid, and their combination to enhance bioavailability and neuroprotective efficacy through improved delivery across the blood–brain barrier (BBB). **Materials and Methods:** Three phytosomal formulations of each resveratrol, syringic acid, and their combination were prepared using different concentrations of phosphatidylcholine (0.5, 1.0, and 2.0%) and evaluated for yield, particle size, polydispersity index (PDI), zeta potential, and encapsulation efficiency (EE). **Results:** All the phytosomal formulations exhibited high percentage yield (92.6–93.3%) and EE (93.3–96%), confirming efficient complex formation of phytoconstituents with phospholipids. The average particle size ranged from 127 to 160 nm with a PDI between 0.13 and 0.22, indicating homogenous nanoparticle dispersion. Zeta potential values between −14.5 mV and +14.5 mV demonstrated good colloidal stability and favorable interaction potential with the BBB. Combination phytosomes achieved EE% of R+S+PC (1:1) (96%), indicating effective co-loading. Particle sizes varied from 215 nm (pure syringic acid) to 157.3 nm (S+PC) (1:0.5), with PDI values of 0.16 to 0.25 indicating moderate to good uniformity, and zeta potentials between 0.3 and 14.5 mV suggested good colloidal stability. Melting point depression in complexes confirmed Drug–Polymer interactions and reduced crystallinity. **Conclusion:** The optimized phytosomal systems displayed excellent physicochemical stability and nanoscale characteristics conducive to enhanced absorption and brain permeability. These findings demonstrate the successful development of resveratrol–syringic acid phytosomal formulation with high EE and good stability that significantly contributes to synergistic neuroprotective delivery in Parkinson's therapy. Further *in vivo* evaluations are necessary to validate their therapeutic efficacy and synergistic mechanisms.

Key words: Dual phytosome, neuroprotection, Parkinson's disease, phosphatidylcholine, preformulation, resveratrol, syringic acid

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the selective loss of dopaminergic neurons in the substantia nigra pars compacta, leading to motor dysfunction, tremors, rigidity, and cognitive decline.[1,2] The current pharmacological interventions, such as levodopa and dopamine agonists, primarily offer symptomatic relief without halting disease progression, and long-term use often results in motor complications.[3-5] The limitations of conventional therapies have driven interest in novel therapeutic strategies, particularly those employing bioactive phytoconstituents with neuroprotective potential.[6-9] Herbal bioactives such as polyphenols,

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flavonoids, and alkaloids have gained significant attention for their neuroprotective, antioxidant, and anti-inflammatory properties, which are crucial in mitigating the pathophysiology of PD.[10-12] However, the clinical translation of these phytoconstituents is severely hampered by their poor aqueous solubility, low membrane permeability, rapid metabolism, and limited bioavailability, especially across the blood–brain barrier (BBB). These limitations necessitate the development of advanced drug delivery systems that can enhance pharmacokinetic profiles and target specificity.

Resveratrol, a stilbene polyphenol found in grapes, berries, and peanuts, has demonstrated significant neuroprotective potential by scavenging reactive oxygen species, modulating mitochondrial function, and attenuating neuroinflammation.[13-16] For PD, it mitigates oxidative damage by activating AMPK, reducing COX-2 activity, lipid peroxidation, and enhancing antioxidant enzyme production. Syringic acid, a naturally occurring phenolic acid present in fruits, cereals, and spices, exhibits complementary mechanisms including potent antioxidant activity, inhibition of lipid peroxidation, and protection against excitotoxicity.[17-19] The combination of resveratrol and syringic acid could offer synergistic neuroprotection by targeting multiple pathological pathways involved in PD progression. However, both compounds suffer individually from poor aqueous solubility, instability in the gastrointestinal tract, rapid metabolism, and limited permeability across the BBB, resulting in low systemic bioavailability and inadequate therapeutic concentrations in the brain. Overcoming these pharmacokinetic limitations is critical for translating their preclinical promise into effective clinical therapy.

Phytosomes, a novel nanocarrier system, have emerged as a promising approach to overcome these challenges. Unlike conventional liposomes, phytosomes are molecular complexes of plant extracts or phytoconstituents with phospholipids, typically phosphatidylcholine (PC), which result in improved lipid compatibility and enhanced absorption.[20-22] The phospholipid component not only facilitates incorporation into biological membranes but also improves stability, bioavailability, and targeted delivery, including potential transport across the BBB.[23,24] Hence, the current study explores nano-preformulation strategies for resveratrol in combination with syringic acid (a hypothetical co-therapeutic agent) using an appropriate carrier, aiming to achieve enhanced bioavailability, BBB penetration, and synergistic therapeutic effects for both PD and Alzheimer's disease. Drug parameters such as solubility, chemical stability, encapsulation efficiency (EE), particle size, zeta potential, and physicochemical characterizations including X-ray diffraction (XRD), Fourier-transform infrared (FT-IR) spectroscopy, and scanning electron microscopy (SEM) were evaluated for the phytosomal formulation in the present work.

MATERIALS AND METHODS

Materials

Resveratrol (≥98% purity) and syringic acid (≥98% purity) were procured from Yucca Enterprises. PC, soya lecithin grade was obtained from Sigma Aldrich. All solvents and reagents, including chloroform, methanol, ethanol, and phosphate buffer salts, were of analytical grade (AR) and purchased locally. Double-distilled water was used throughout the study.

Preformulation studies

The preformulation studies were carried as follows:[25,26]

Organoleptic properties

Resveratrol and syringic acid were examined visually for color, odor, and appearance.

Solubility

The solubility of resveratrol and syringic acid was determined in distilled water, ethanol, methanol, 0.1N HCl, and phosphate buffer (pH 6.8). Excess drug was added to 5 mL solvent, sonicated for 10 min, and kept at 37 ± 0.5°C for 24 h. After equilibrium, samples were centrifuged (10,000 rpm, 10 min), filtered (0.22 μm), and analyzed spectrophotometrically at their respective λ-max.

Melting point

The melting points were determined by the capillary method using a digital melting point apparatus. A fused capillary containing a small amount of powdered sample was placed in the apparatus and the temperature at which the sample melted was recorded.

Partition coefficient (log P)

The shake-flask method was used with n-octanol and water (pH 7.4). Drug concentrations in both phases were determined by ultraviolet (UV) spectrophotometry.

λ-max determination and calibration curve

For each drug, a 10 μg/mL solution was scanned between 200 and 400 nm in a double-beam UV-visible spectrophotometer to determine λ-max. Calibration curves were prepared in phosphate buffer (pH 6.8) in the range of 10–50 μg/mL.

Drug–excipient compatibility studies

FT-IR spectroscopy was employed to detect possible interactions between the drugs and PC. Samples were analyzed for characteristic peaks, and any shifts or disappearance of peaks were noted.

Preparation of phytosomal formulations

Phytosomes containing resveratrol (R), syringic acid (S), or their combination were prepared by the solvent evaporation method [Tables 1-3].[24,25] PC was dissolved in 50 mL of dichloromethane, while the combined resveratrol (R) and syringic acid (S) were diluted in 100 mL of 50% ethanol. The solution was then combined using magnetic stirrer and was heated to 25°C for 8 h. Then, ethanol and dichloromethane were removed using a rotary evaporator at 45°C for 3 h. The final solution was frozen at −80°C overnight and dried by using lyophilization for 48 h. The dry sample was packed and stored in a desiccator containing silica gel at 4°C for further use.

Characterization of phytosomes

Percentage yield

The percentage yield was calculated from the total weight of dried phytosomes obtained compared to the theoretical weight of the drug and excipients.

$$\% \text{ Yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

EE%

A known weight of phytosomes was dissolved in phosphate buffer with intermittent shaking for 24 h, followed by filtration. Drug content in the filtrate was determined spectrophotometrically, and EE% was calculated.

$$\% \text{ Drug content} = \frac{\text{Amount of drug present in formulation}}{\text{Calculated amount in formulation}} \times 100$$

$$\% \text{ Entrapment efficiency} = \frac{\text{Drug added} - \text{free or untraped drug}}{\text{Drug added}} \times 100$$

Particle size, zeta potential, and PDI

Measurements were performed using a dynamic light scattering instrument (Zetasizer). Samples were diluted with distilled water before analysis.

Melting point of complexes

The melting points of drug–PC complexes were determined to confirm complex formation, with possible shifts from pure drug melting points.

XRD analysis

XRD was done on pure phytocompounds and phytosomal formulations in different ratios of drug and PC to see crystallinity in the substance and possible amorphization after complexation. Sample was scanned in the angular range of 10–80° in an Aeris-Panalytical instrument. Dried powder sample was kept in sample holder (20 mm × 15 mm × 2 mm) which was fitted into the instrument, and X-ray was passed through the sample.

FT-IR analysis

FT-IR was used to identify functional groups and drug–lipid interactions. FT-IR studies were performed with Alpha FT-IR spectrophotometer (Bruker, Germany). A small quantity of sample was placed just below the probe onto which the probe was tightly fixed and scanned in the wave number region 4000–500 cm^{-1}. The obtained IR spectra were interpreted for functional groups and drug–lipid interactions at their respective wave number (cm^{-1}).

Table 1: Formulations for resveratrol phytosome

Formulation code	Resveratrol (mg)	Phosphatidylcholine (mg)	Phytosome ratio
RF-1	500	250	1:0.5
RF-2	500	500	1:1
RF-3	500	1000	1:2

Table 2: Formulations for syringic acid phytosome

Formulation code	Syringic acid (mg)	Phosphatidylcholine (mg)	Phytosome ratio
S F-1	500	250	1:0.5
S F-2	500	500	1:1
SF-3	500	1000	1:2

Table 3: Formulations for resveratrol+syringic acid phytosome

Formulation code	Resveratrol(mg)	Syringic acid(mg)	Phosphatidylcholine(mg)	Phytosome ratio
R+S F-1	250	250	250	1:0.5
R+S F-2	250	250	500	1:1
R+S F-3	250	250	1000	1:2

SEM

Morphology was studied using SEM to assess particle surface and structural organization. Analysis was done on the coated sample by placing a pinch of the sample in the Carl Zeiss (Gemini 560) scanning electron microscope, and surface morphology was viewed and photographed.

RESULTS AND DISCUSSION

Preformulation studies

Resveratrol was obtained as an off-white crystalline powder with a melting point of 259°C, while syringic acid appeared as a fine, light-brown powder with a melting point of 212°C. Both drugs exhibited good solubility in methanol and ethanol, moderate solubility in phosphate buffer (pH 6.8) and 0.1 N HCl, and poor solubility in distilled water, consistent with their hydrophobic nature. Partition coefficient values indicated lipophilicity suitable for complexation with PC. λ-max values were determined at 304 nm for resveratrol and 262 nm for syringic acid, which were used for subsequent UV-based quantifications [Figure 1].

Phytosome preparation, yield, and EE%

Phytosomes were successfully prepared for resveratrol alone (R+PC), syringic acid alone (S+PC), and their combination (R+S+PC) at three molar ratios (1:0.5, 1:1, and 1:2) (drug:PC). The percentage yield varied across formulations [Table 4]. R+PC formulations showed yields between 50.3% and 93.3%, with the highest yield (93%) observed at the (RF2) 1:1 ratio. S+PC phytosomes exhibited yields between 40.6% and 92.6%, with the highest yield at SF1 1:0.5 ratio. Combination formulations (R+S+PC) had yields ranging from 69.8% to 93.3%, with the (R+S F1) 1:0.5 ratio achieving the best recovery. Lower yields in certain batches (e.g., S+PC SF-2) could be attributed to drug loss during hydration or incomplete incorporation into the lipid bilayer. EE values ranged from 85.6% to 96% across all formulations. For single-drug phytosomes, R+PC phytosome RF-2 (1:1 ratio) achieved the highest EE% (93.6%), with enhanced drug entrapment, likely by providing more binding sites for hydrophobic interactions and hydrogen bonding. Similarly, S+PC phytosome SF-1 showed an EE% of 93.3%, outperforming lower PC ratios. In the combination formulations, EE% was relatively stable (86.6–96%), suggesting that both drugs could be co-loaded effectively without significant competitive displacement during complexation, and the results are displayed in Table 4. Hence, we experimentally adjust the stoichiometric ratio of active constituents and phospholipids to have the highest drug loading.[27]

Particle size, zeta potential, PDI, and melting point analysis

Particle size analysis revealed that pure resveratrol formed particles of 635 nm, while syringic acid alone formed much smaller particles (215 nm), reflecting differences in crystallinity and molecular structure [Figure 2 and Table 5]. Complexation with PC significantly altered particle dimensions:

- R+PC complexes ranged from 160.8 nm (RF2) to slightly smaller values at higher PC concentrations
- S+PC complexes averaged 155.3nm (S F1)
- R+S+PC complexes were 127.0 nm (R+S F1)

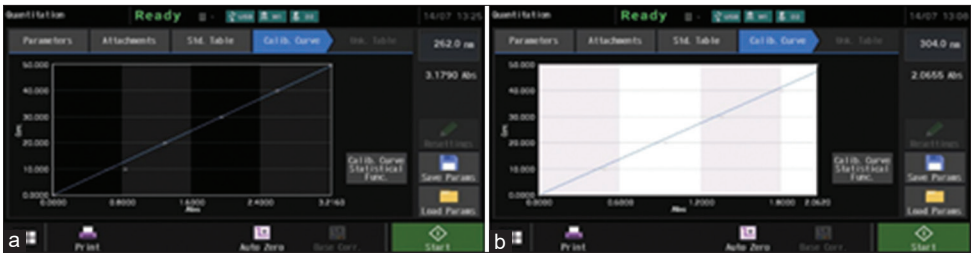

Figure 1: Calibration curve of resveratrol (a) and syringic acid (b)

Table 4: Percentage yield and encapsulated efficiency of phytosomal formulation

Formulation code	Ratios	Percentage yield(%)	Encapsulation efficiency(%)	Percentage of drug content
R F-1	1:0.5	50.3±1.64	86±173	93.6±0.83
R F-2	1:1	93.3±1.83	93.6±1.64	98.7±1.1
R F-3	1:2	68±2.64	90.6±1.64	95±1.04
S F-1	1:0.5	92.6±1.64	93.3±1.83	84.6±0.83
S F-2	1:1	40.6±2.47	85.6±2.38	73.7±1.3
S F-3	1:2	54±2	91.8±1.61	65.3±1.16
R+S F-1	1:0.5	93.3±1.83	96±1.41	87.8±0.77
R+S F-2	1:1	79.3±2.08	86.6±2.16	45±0
R+S F-3	1:2	69.8±1.81	88.6±2.38	20±0

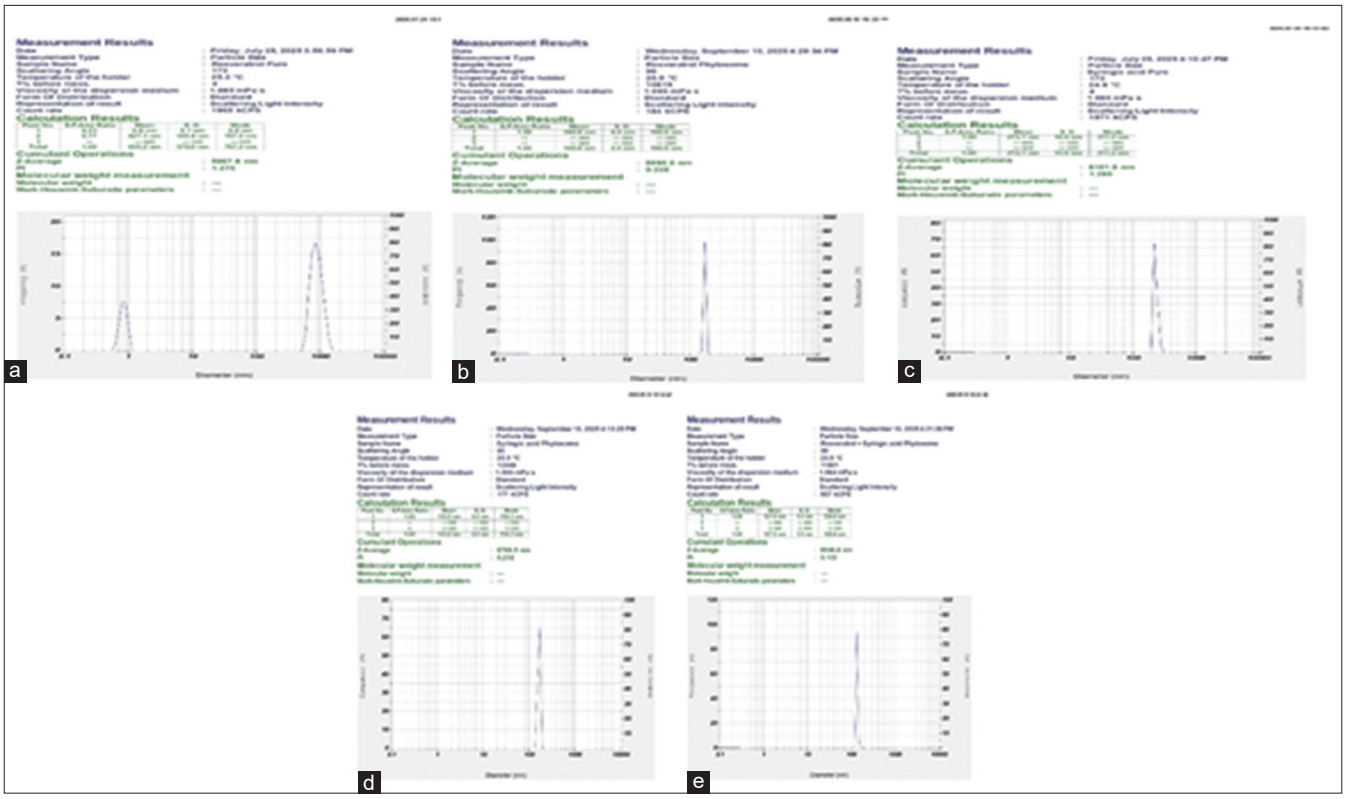

Figure 2: Particle size and poly dispersity index of resveratrol pure (a), resveratrol phytosome (b), syringic acid pure (c), syringic acid phytosome (d), and resveratrol + syringic acid phytosome formulation (e)

Table 5: Characterization of phytosomal formulation

Formulation	Particle size(nm)	Zeta potential(mV)	Polydispersity index	Melting point
Resveratrol(R)	633±2.16	−17.1±1.802	2.05±1.02	260.6±1.51
Syringic acid(S)	219±1.41	−63.4±3.65	1.80±0.72	216.6±2.16
R F-1	176.6±2.5	+17±0.86	0.27±0.26	257±1.71
R F-2	159.3±2.7	+17.5±0.77	0.14±0.14	255.6±2.38
R F-3	176.3±3	+17.5±0.89	0.32±0.17	259±2
S F-1	157.3±2.7	+18.3±1	0.22±0.14	208.6±1.3
S F-2	176.6±2.7	+17.6±0.86	0.27±0.2	208±1.41
S F-3	172.6±3.1	+17.9±0.5	0.30±0.2	208.3±1.62
R+S F-1	154.3±1.8	+18.2±0.89	0.16±0.17	199±2
R+S F-2	173±2.6	+13.3±1.5	0.20±0.14	202.3±1.73
R+S F-3	182.6±3.2	+16.3±2.7	0.25±0.2	206.3±1.62

Zeta potential values ranged from −4.3 mV for pure resveratrol and 0.3 mv for resveratrol phytosome, −67.1 mv for pure syringic acid and −0.3 mv for syringic acid phytosome, and the zeta potential of resveratrol and syringic acid phytosome (R+S) shifted to +14.5mV [Figure 3]. Since negatively charged endothelial membranes are attracted to it, a positive shift in zeta potential improves adsorptive-mediated transport across the BBB. To balance systemic stability, safety, and brain uptake, an ideal moderate positive charge is essential [Table 5].[28]

PDI data revealed that PDI values of resveratrol pure are 1.27, resveratrol phytosome are 0.22, syringic acid pure are 1.28, syringic acid phytosome are 0.21, and the PDI values of resveratrol + syringic acid phytosome are 0.13, suggesting that dual loading promoted more uniform particle distribution [Figure 2 and Table 5].

The melting points of resveratrol pure are 259, resveratrol phytosome are 257°C, syringic acid pure are 212°C, syringic acid phytosome are 209°C, and the PDI of resveratrol+ syringic acid phytosome are 195°C, indicating successful formation of amorphous or less crystalline complexes. This reduction is consistent with molecular dispersion of the drugs within the phospholipid matrix.[22]

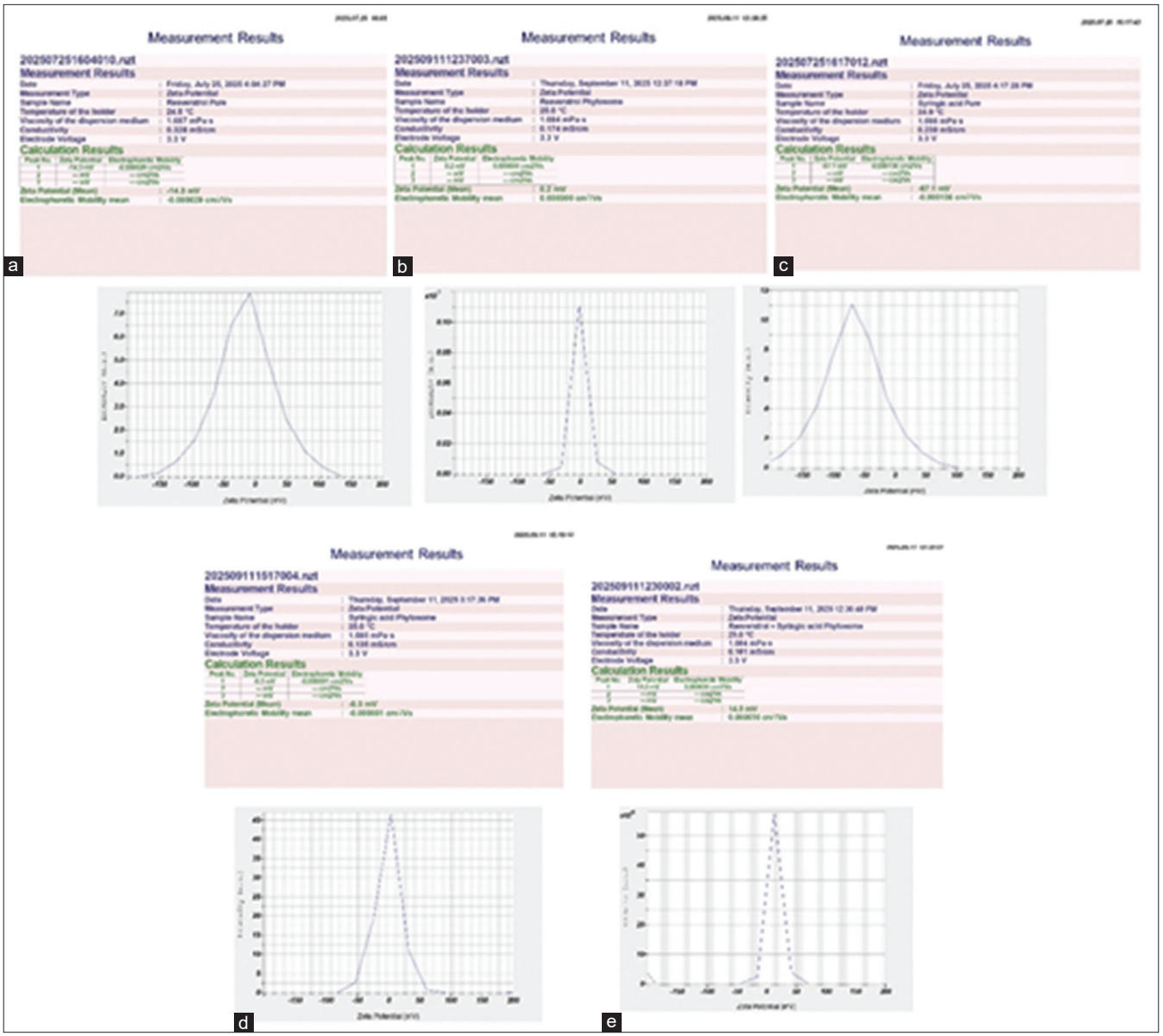

Figure 3: Zeta potential of resveratrol pure (a), resveratrol phytosome (b), syringic acid pure (c), syringic acid phytosome (d), and resveratrol + syringic acid phytosome formulation (e)

Physicochemical characterization of formulation

XRD study

Powder XRD patterns of the resveratrol (R) and syringic acid (S) containing formulations are shown in Figure 4. Resveratrol and syringic acid formulation (R-F1, S-F3) display multiple sharp diffraction peaks in the 10–30° 2θ range, indicating well-ordered crystalline phases. In contrast, several formulations (R-F2, R-F3) exhibit a pronounced loss of sharp peaks and the appearance of broad peaks consistent with conversion to an amorphous or highly dispersed state upon formulation with PC formulation. S-F2 and S-F3 show reduced peak intensity and peak broadening relative to S-F3, indicating partial disruption of crystallinity.

Powder XRD patterns for pure resveratrol, pure syringic acid, and the physical mixture (R+S+PC) and three formulation variants (R+SF1, R+SF2, R+S F3) are shown in Figure 5**.** The drugs show multiple sharp reflections between 10° and 32° 2θ, indicative of well-ordered crystalline phases. The physical mixture retains these diagnostic peaks, whereas the formulated samples display progressive attenuation and broadening of drug peaks: R+SF2 and R+SF3 show reduced peak intensities and peak broadening (partial loss of crystallinity), while R+S F1 exhibits an amorphous or molecularly dispersed drug of the active components within the formulation matrix, which is expected to enhance dissolution rate and bioavailability.[25,29-31]

FT-IR spectroscopy

The FT-IR spectra of pure compounds resveratrol and syringic acid, their individual formulations (RF1 to RF3, SF1 to SF3), the physical mixture (R+S+PC), and

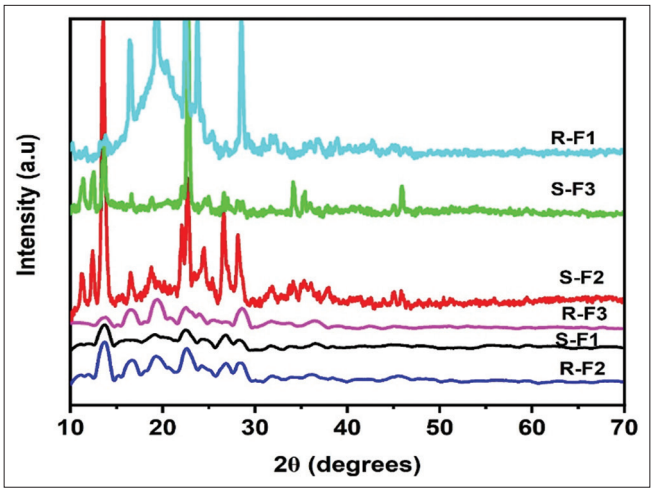

Figure 4: X-ray diffraction patterns of formulations with resveratrol (r) and syringic acid (s)

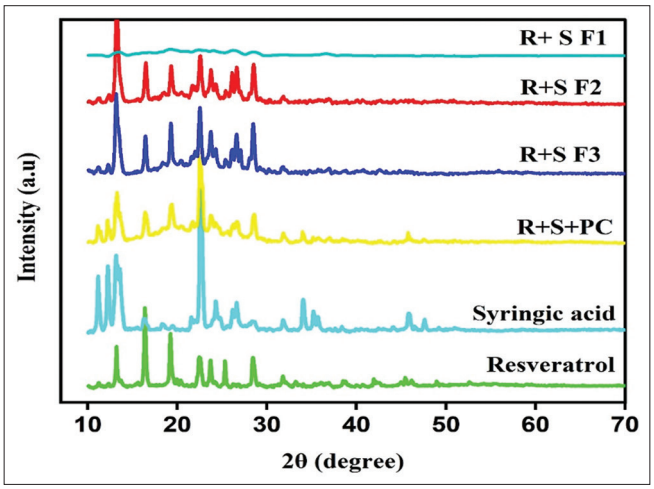

Figure 5: X-ray diffraction patterns of formulations which include combination of resveratrol and syringic acid, with varying the concentration of phosphatidylcholine

combined formulations (R+SF1 to F3 shown in Figure 6) were recorded to investigate the molecular interactions and confirm encapsulation with PC. Resveratrol and syringic acid show that similar broad O–H stretching vibration band was observed around 3300–3400 cm^{-1}, confirming the presence of phenolic hydroxyl groups. The aromatic C–H stretching band appeared at 2933 cm^{-1}, while the C=C stretching vibration of the aromatic ring was detected at 1695 cm^{-1}. Peaks at 1110 cm^{-1} and 825 cm^{-1} correspond to C–O stretching and aromatic C–H bending, respectively. All formulations retained the primary characteristic peaks of resveratrol and syringic acid, though with noticeable broadening and slight shifts in wavenumber, indicating hydrogen bonding and interaction with the PC carrier. The spectrum of the physical mixture showed the superimposed peaks of resveratrol and syringic acid along with PC, without major shifts, confirming the absence of strong chemical bonding in the physical blend. The combined formulations (R+SF1, R+S F2, and R+S F3) showed significant peak broadening and reduced intensity of the phenolic O–H stretch (~3390 cm^{-1}), indicating hydrogen bonding interactions between drug molecules and PC. The C–H stretching band near 2933 cm^{-1} became less pronounced in R+SF1 and R+SF2, while the C=C stretching band (~1695 cm^{-1}) showed diminished sharpness compared to pure compounds. Fingerprint region peaks (1110 cm^{-1} and 825cm^{-1}) also appeared diffused, suggesting successful encapsulation and amorphization of the active compounds.[32,33]

SEM analysis

SEM images reveal the morphological characteristics of various formulations, as shown in Figure 7. The presence of rod-like or needle-like structures indicates the initial stages of phytosome development.[33,34] The low polymer concentration facilitates the observation of distinct, elongated shapes, suggesting possible interactions between

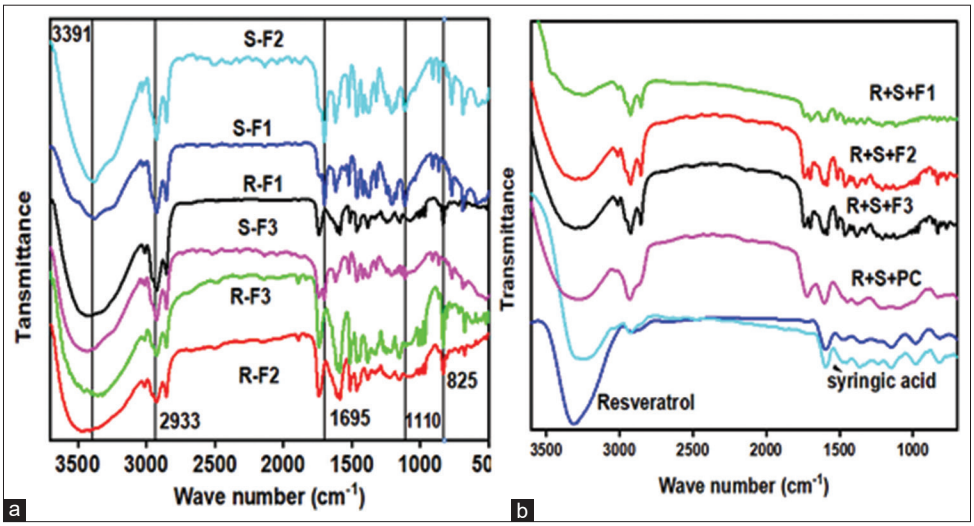

Figure 6: Fourier-transform infrared spectra for (a) formulations with resveratrol (r) and syringic acid (s), (b) formulations which include combination of resveratrol, syringic acid with varying the concentration of phosphatidylcholine

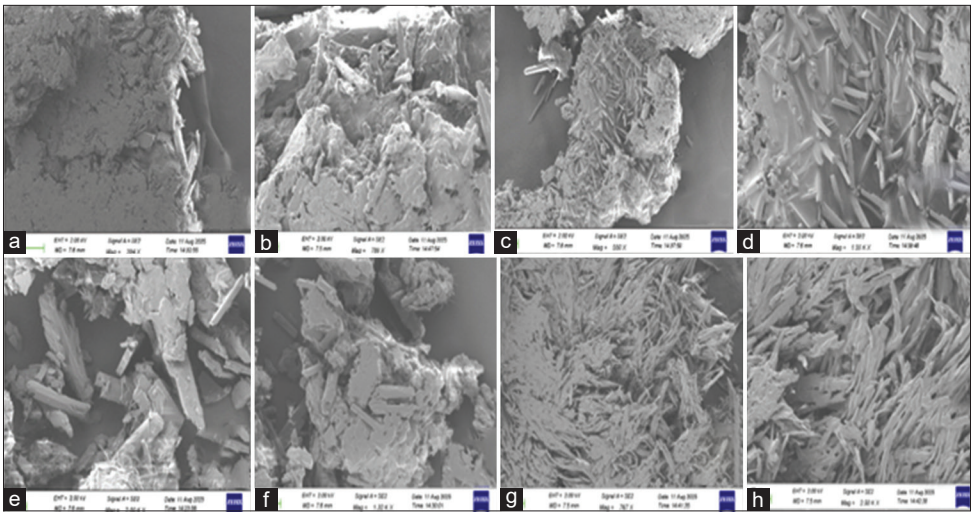

Figure 7: Scanning electron microscopy images illustrating the morphological characteristics of various formulations: (a) Syringic acid formulation (SF1), (b) Resveratrol formulation (RF2), (c and d) Phytosomal formulation (R+S F1), (e and f) Phytosomal formulation (R+S F2), and (g and h) Phytosomal formulation (R+S F3)

resveratrol, syringic acid, and the lipid matrix. In contrast, the other formulations exhibit hard, bundle-like structures and particle agglomeration, lacking further development of well-separated structures. These electron microscopic images imply that formulations SF1, RF2, R+SF2, and R+SF3 may not represent the optimal stoichiometric combinations for achieving high-quality formulations.

From the above results, three different types of formulations for each phytosome were prepared using different concentrations of PC (0.5, 1.0, and 2.0) with resveratrol, syringic acid, and their combinations, respectively, were evaluated under various parameters that include yield, particle size, and EE. For all the formulations, the highest yield was 92.6–93.3% and EE was 93.3–96% that confirm the efficiency of the phospholipid complexation process, ensuring maximum entrapment of bioactive compounds within the vesicular system. This was supported by XRD, FT-IR, and SEM characterization studies. On the other hand, the obtained nanoscale particle size range (127–160 nm) and fine PDI (0.13–0.22) indicate uniform and stable dispersions suitable for enhanced bioavailability and brain targeting. Moreover, the zeta potential values (−14.5 mV to +14.5 mV) suggest sufficient colloidal stability and favorable interaction with the negatively charged endothelial membranes of the BBB.

CONCLUSION

The prepared phytosomal formulations of resveratrol, syringic acid, and their combination demonstrated excellent physicochemical characteristics, reflecting their strong potential for neuroprotective drug delivery applications. Collectively, the research findings in this work highlight that the optimized phytosomal formulations can significantly enhance the solubility, stability, and permeability of the dual phytosome formulation made of resveratrol and syringic acid, thereby overcoming their conventional delivery limitations of each drug separately. In precise, the optimized formulation R+S F1 demonstrated high EE, reduced crystallinity, stable zeta potential, and favorable morphology. Such improved pharmacokinetic behavior positions these dual phytosomal systems as promising candidates for the management and prevention of neurodegenerative disorders like PD, where oxidative stress and mitochondrial dysfunction play critical roles. Further *in vitro* and *in vivo* neuroprotective studies are needed to validate their therapeutic efficacy and mechanism of action.

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AUTHOR'S CONTRIBUTIONS

B. Ramya Kuber: Writing–review and editing, supervision, project administration, methodology, conceptualization, and funding. Pinapeddavari Narasimhulu Mayuri: Writing–review, validation, methodology, investigation, formal analysis, data curation, conceptualization, funding. N. Varalakshmi: Validation, methodology, investigation, formal analysis, data curationand funding. J. Jyothirmayi: Methodology, investigation, formal analysis, data curation.

REFERENCES

1. Dauer W, Przedborski S. Parkinson's disease: Mechanisms and models. Neuron 2003;39:889-909.
2. Kalia LV, Lang AE. Parkinson's disease. Lancet 2015;386:896-912.
3. Olanow CW, Stern MB, Sethi K. The scientific and clinical basis for the treatment of Parkinson disease (2009). Neurology 2009;72:S1-36.
4. Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. Nat Rev Neurosci 2017;18:435-450.
5. Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov Disord 2001;16:448-58.
6. Yan L, Guo MS, Zhang Y, Yu L, Wu JM, Tang Y, *et al*. Dietary plant polyphenols as the potential drugs in neurodegenerative diseases: Current evidence, advances, and opportunities. Oxid Med Cell Longev 2022;2022:5288698.
7. Gahtani RM, Shoaib S, Hani U, Jayachithra R, Alomary MN, Chauhan W, *et al*. Combating Parkinson's disease with plant-derived polyphenols: Targeting oxidative stress and neuroinflammation. Neurochem Int 2024;178:105798.
8. Arias-Sánchez RA, Torner L, Fenton Navarro B. Polyphenols and neurodegenerative diseases: Potential effects and mechanisms of neuroprotection. Molecules 2023;28:5415.
9. Uttara B, Singh AV, Zamboni P, Mahajan RT. Oxidative stress and neurodegenerative diseases: A review of upstream and downstream antioxidant therapeutic options. Curr Neuro Pharmacol 2009;7:65-74.
10. Solanki I, Priyanka P, Mansuri ML, Mordhwaj SP. Flavonoid-based therapies in the early management of neurodegenerative diseases. Adv Nut 2015;6: 64-72.
11. De Lima EP, Laurindo LF, Catharin VC, Direito R, Tanaka M, JasminSG, *et al*. Polyphenols, alkaloids, and terpenoids against neurodegeneration: Evaluating the neuroprotective effects of phytocompounds through a comprehensive review of the current evidence. Metabolites 2025;15:124.
12. Ramassamy C. Emerging role of polyphenolic compounds in the treatment of neurodegenerative diseases: A review of their intracellular targets. Eur J Pharmacol 2006;545:51-64.
13. Singh N, Agrawal M, Dore S. Neuroprotective properties and mechanisms of resveratrol in *in vitro* and *in vivo* experimental cerebral stroke models. ACS Chem Neurosci 2013;4:1151-62.
14. Bastianetto S, Ménard C, Quirion R. Neuroprotective action of resveratrol. Biochim Biophys Acta 2015;1852:1195-201.
15. Rocha-González HI, Ambriz-Tututi M, Granados-Soto V. Resveratrol: A natural compound with Pharmacological potential in neurodegenerative diseases. CNS Neurosci Ther 2008;14:234-47.
16. Ma X, Sun Z, Liu Y, Jia Y, Zhang B, Zhang J. Resveratrol improves cognition and reduces oxidative stress in rats with vascular dementia. Neural Regen Res 2013;8:2050-9.
17. Zhao Z, Yang Q, Sun Y, Ruan X. Unveiling the antioxidant and anti-inflammatory potential of syringic acid: Mechanistic insights and pathway interactions. Front Pharmacol 2025;16:1615294.
18. Cikman O, Soylemez O, Ozkan OF, Kiraz HA, Sayar I, Ademoglu S, *et al*. Antioxidant activity of syringic acid prevents oxidative stress in l-arginine-induced acute pancreatitis: An experimental study on rats. Int Surg 2015;100:891-6.
19. Bartel I, Mandryk I, Horbańczuk JO, Wierzbicka A, Koszarska M. Nutraceutical properties of syringic acid in civilization diseases-review. Nutrients 2024;16:10.
20. Talebi M, Kimia S, Dakkali MS, Akbari M, Ghale RA, Hashem S, *et al*. Phytosomes: A promising nanocarrier system for enhanced bioavailability and therapeutic efficacy of herbal products. Phytomed Plus 2025;5100779.
21. Kidd PM. Bioavailability and activity of phytosome complexes from botanical polyphenols: The silymarin, curcumin, green tea, and grape seed extracts. Altern Med Rev 2009;14:226-46.
22. Lu M, Qiujun Q, Luo X, Liu X, Sun J, Wang C, *et al*. Phyto-phospholipid complexes (phytosomes): A novel strategy to improve the bioavailability of active constituents. Asian J Pharm Sci 2019;14:265-74.
23. Bombardelli E, Spelta M. Phospholipid-polyphenol complexes: A new concept in skin care ingredients. Cosmet Toilet 1991;106:69-76.
24. Di Costanzo A, Angelico R. Formulation strategies for enhancing the bioavailability of silymarin: The state of the art. Molecules 2019;24:2155.
25. Semalty A, Semalty M, Rawat MS, Franceschi F. Supramolecular phospholipid-polyphenolic interactions: The phytosome strategy to improve the bioavailability of phytochemicals. Fitoterapia 2010;81:306-14.
26. Ajazuddin, Saraf S. Applications of novel drug delivery system for herbal formulations. Fitoterapia 2010;81680-89.
27. Kalita B, Das MK. Resveratrol-phospholipid complexes (phytosomes) with improved physicochemical properties favorable for drug delivery via skin. World J Pharm Res 2015;4:1497-517.
28. Das MK, Kalita B. Design and evaluation of phyto-phospholipid complexes (phytosomes) of rutin for transdermal application. J Appl Pharm Sci 2014;4:51-7.
29. Sun R, Zhao G, Ni S, Xia Q. Lipid based nanocarriers with different lipid compositions for topical delivery of resveratrol: Comparative analysis of characteristics and performance. J Drug Deliv Sci Technol 2014;24:591-600.
30. Saraiva C, Praça C, Ferreira R, Santos T, Ferreira L,

Bernardino L. Nanoparticle-mediated brain drug delivery: Overcoming blood-brain barrier to treat neurodegenerative diseases. J Control Release 2016;235:34-47.
31. Rajesh T, Sudhir M, Sowjanya T, Ashwini N, Naidu VG, Nalini RS. Syringic acid: Structural elucidation and Co-crystallization. Cryst Growth Des 2016;16:4679-87.
32. Van den Mooter G. The use of amorphous solid dispersions: A formulation strategy to overcome poor solubility and dissolution rate. Drug Discov Today Technol 2012;9:e79-85.
33. Rasheed A, Kamran SH, Hameed M, Siddique F, Latif S, Bibi M, *et al*. Syringic acid loaded chitosan nanoparticles mitigate glycation associated oxidative stress and inflammation in hyperglycaemic rat model. Sci Rep 2025;15:22778.
34. Argenziano M, Ansari IA, Muntoni E, Spagnolo R, Scomparin A, Cavalli R. Lipid-coated nanocrystals as a tool for improving the antioxidant activity of resveratrol. Antioxidants (Basel) 2022;11:1007.

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