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ORIGINAL ARTICLE

QBD-Based Preparation, Pre-Formulation Studies, and Characterization of Resveratrol-Loaded Nanophytosomes

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ABSTRACT
Plant-derived materials are increasingly gaining attention as dietary supplements due to their broad spectrum of medicinal applications. Among these, resveratrol polyphenolic flavonoid-has emerged as a potent antioxidant capable of scavenging superoxide radicals. It is considered a vital nutraceutical owing to its ability to strengthen and modulate the permeability of blood vessel walls. However, despite its therapeutic potential, resveratrol suffers from poor aqueous solubility and limited oral bioavailability, posing significant challenges for its effective clinical application. The objective of the present study was to formulate and characterize a stable resveratrol-loaded nanophytosomal system aimed at improving its antioxidant efficacy and enhancing its bioavailability via lymphatic transport. The resveratrol–phospholipid complex (RPC) was developed using the lipid hydration technique and characterized using Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC). Furthermore, X-ray Diffraction (XRD) studies confirmed the formation of the nanophytosome complex. A Quality-by-Design (QbD) approach was employed for systematic development, allowing optimization within a defined design space to ensure formulation robustness and enhanced lymphatic targeting. The findings demonstrated that the self-emulsifying nanophytosomal formulation significantly improved the physicochemical characteristics of resveratrol, facilitating better absorption and transport through the intestinal lymphatic system. These results suggest that nanophytosomes serve as an efficient carrier system for fortifying herbal medicinal compounds. Therefore, such delivery systems can be effectively employed in the development of functional foods and pharmaceutical formulations, enhancing both therapeutic efficacy and patient compliance.
Keywords: *Resveratrol, Nanophytosome, Lymphatic Transport, Quality by Design, Herbal Drug Delivery.*

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INTRODUCTION

Resveratrol (3, 4, 5-trihydroxystilbene) is a stilbenoid class of compound and works as phytoalexin (i.e., a substance that is produced by plant tissues in response to contact with a parasite and specifically inhibits the growth of that parasite) [1]. Because of its intriguing pharmacological potential, it has recently gained a lot of study attention. Early studies have illustrated the presence of substantial amounts of Resveratrol in wounded, infected, and UV-treated leaves [2]. It is primarily found in grapes, peanuts, and berries. In the 1940s, Resveratrol was discovered in the white hellebore plant. It is also found in processed plant products; its presence in red wine (concentrations of 0.1–14.3 mg/L) has been proposed as a possible explanation for the "French paradox," the observation of an unusually low rate of heart disease among Southern French people who drink a lot of red wine, despite a high saturated fat diet [3,4]. SIRT1, one of the mammalian versions of the sirtuin family of proteins, is activated by Resveratrol, deacetylates histones and non-histone proteins, such as transcription factors. Metabolism, stress resistance, cell survival, cellular senescence, inflammation-immune function, endothelial functions, and circadian rhythms are all affected by the SIRT1-regulated pathway [5-7]. Since Resveratrol has been demonstrated

to activate SIRT1, it is expected to help people with disorders such as improper metabolic regulation, inflammation, and cell cycle abnormalities. Resveratrol's usage as a nutraceutical and a therapeutic agent for a variety of disorders has been extensively investigated in preclinical trials as a natural molecule. Moreover, clinical trials have been conducted globally to establish its therapeutic efficacy for the treatment of different diseases [8-11]

To the best of our knowledge, no study to date reports nanotechnological formulations with Resveratrol for in vivo anti-obesity activity. The Phytosomes were prepared by the Lipid Hydration Technique using Phosphatidylcholine**.** To optimize the Phytosomes formulation and its process, the relation between the components of the formulation and process variables was studied and optimized by adopting the QbD principles [12]. The optimized formulation was subjected to a deep physicochemical investigation in terms of particle size, polydispersity index (PDI), pH, viscosity, and osmolarity. Stability studies of up to 60 days at different storage conditions were carried out.

MATERIAL AND METHODS

For the preparation of phytosomes, Phosphatidyl Choline was purchased from Trexgenics India Pvt Ltd. All the solvents were purchased from Merck India Pvt Ltd. Micronized Resveratrol (90% purity) was used as the active ingredient (Yucca Pharmaceuticals, India).

Experimental Design

The central composite design (CCD) 2-level 2-factor was used to find the suitable variables. The selection of independent variables is indicated in Table 1. With the selected levels, a total of thirteen experimental runs were executed. The application of the CCD to establish the relationship between the independent and dependent variables and to optimise the formulation led to a total of thirteen formulations, and the outcomes are summarised in Table 1. Two level two-factor central composite design response surface methodology was employed using Design-Expert software (Trial Version 11.1.2.0, Stat-Ease Inc., MN).

Table 1: Central composite design for optimization of resveratrol Phytosomes

Types Of Variables	Variables	Units	Optimised Levels Used	
			Low Level (-1)	High Level (+1)
In Dependent	PC: Drug (Ratio) (F1) - A	-	0.25:1	2.0:1
	Temperature (F2) – B	^{0}C	50	70
Dependent	Entrapment Efficiency (R1)	%	Maximise	
	Particle Size (R2)	nm	Minimise	
	Zeta Potential (R3)	mV	Minimise	

Effect of Independent Factors on Entrapment Efficiency (%); Particle Size (nm); Zeta Potential (mV). Thirteen experimental runs were conducted to optimize the drug content and stirring rate on Phytosome Entrapment Efficiency (%); Particle Size (nm); Zeta Potential (mV). From the study, particle size ranged from 150 to 510nm, Zeta potential from -71 to -28.32, and entrapment efficiency from 59 to 91%. The table presents the data of CCD experimental runs.

RESULT AND DISCUSSION

Response Analysis through Polynomial Equations

Effect of Variables on Particle Size Data were analysed to fit full second-order quadratic or cubic polynomial equations with added interaction terms to correlate the various studied responses with the examined variables [13-15]. As depicted in 2D and 3D plots (Figures 2&3), it is indicated that at increase in Critical material attributes like Drug: PC Ratio shows an increase in entrapment efficiency and particle size with decrease in zeta potential. Similarly, upon increasing the Critical Process Parameter like Temperature, it shows a decrease in particle size, entrapment efficiency with increase in Zeta potential. It may due to the relaxation of polymer chain which leads to poor drug entrapment in phytosomes. Thus, the lowest levels Drug: PC Ratio was resulted in a minimum particle size. The final mathematical model in terms of coded factors as determined by the Design Expert software is shown below polynomial Equation for particle size, entrapment efficiency, and zeta potential as shown in Table 2.

Response 1: Entrapment Efficiency, Y1

$Y1 = 78.64 + 16.54\ X1 - 4.56X2 - 12.18X1X2$

Response 2: Particle Size, Y2

$Y2 = 224.58 - 47.84X1 - 12.72X2 - 2.24X1X2$

Response 3: Zeta potential, Y3

$Y3 = -35.68 + 12.24X1 - 20.12X2 - 16.24\ X1X2$

ANOVA was applied to determine the significance and the magnitude of the effects of the main variables and the interaction between variables. The results confirm the adequacy of the models (P value <0.05). It identified the significant factors that affect the responses 1, 2, and 3 of Phytosome. The ANOVA result is inbuilt; p-values less than 0.0500 indicate that model terms are significant, as shown in Table 2. Model terms A and B are significant model terms, and a model F-value of 126.54 implies that the model is important [16-18]. The values of the predicted determination coefficient (R^2) and adjusted R^2 were 0.9645 for entrapment efficiency, 0.8177 for Particle size, and 0.9908 for Zeta potential, respectively.

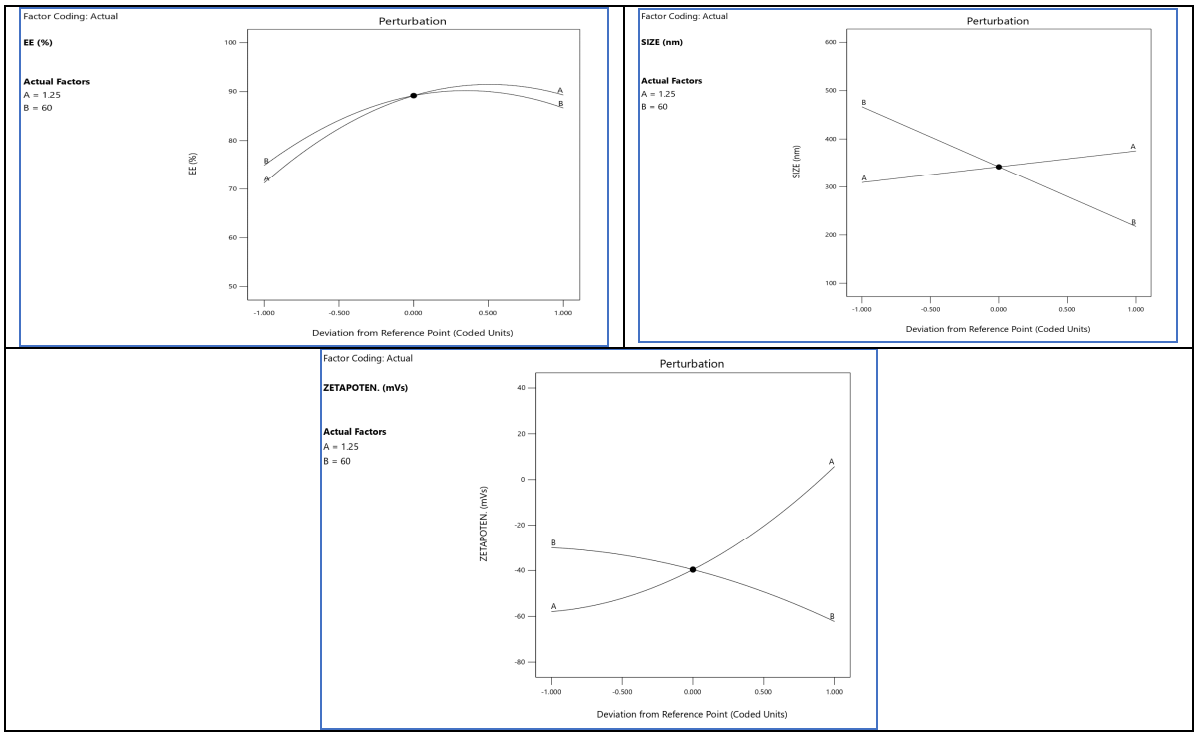
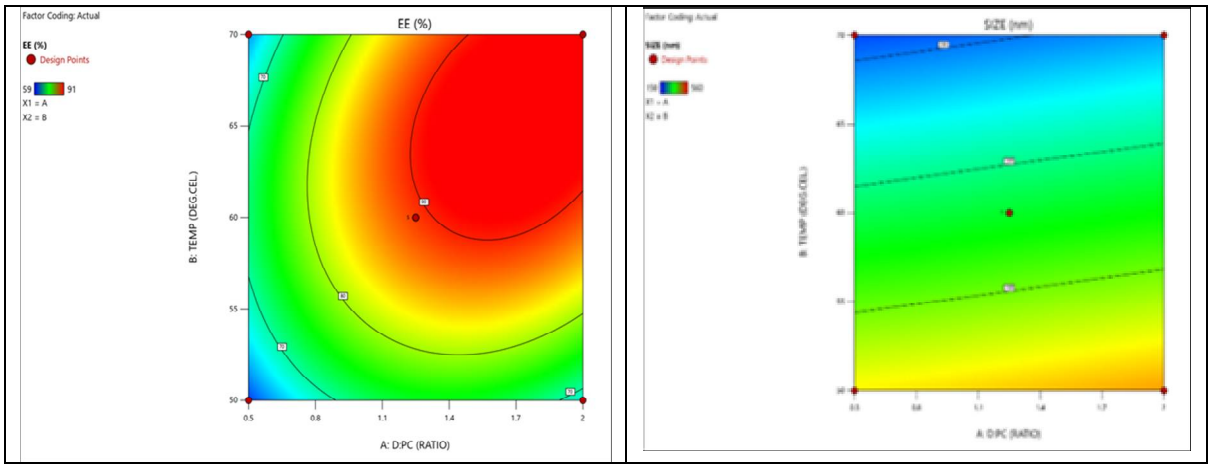


Figure 1: Perturbation plots showing the effect of factors on responses



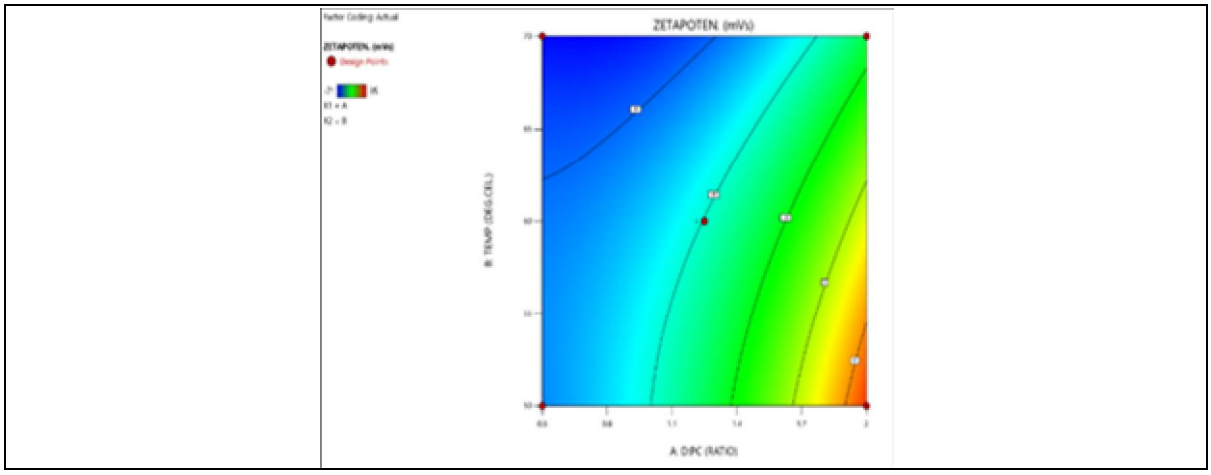


Figure 2: 2D Response surface showing the effect of factor A & B on responses R1, R2, R3

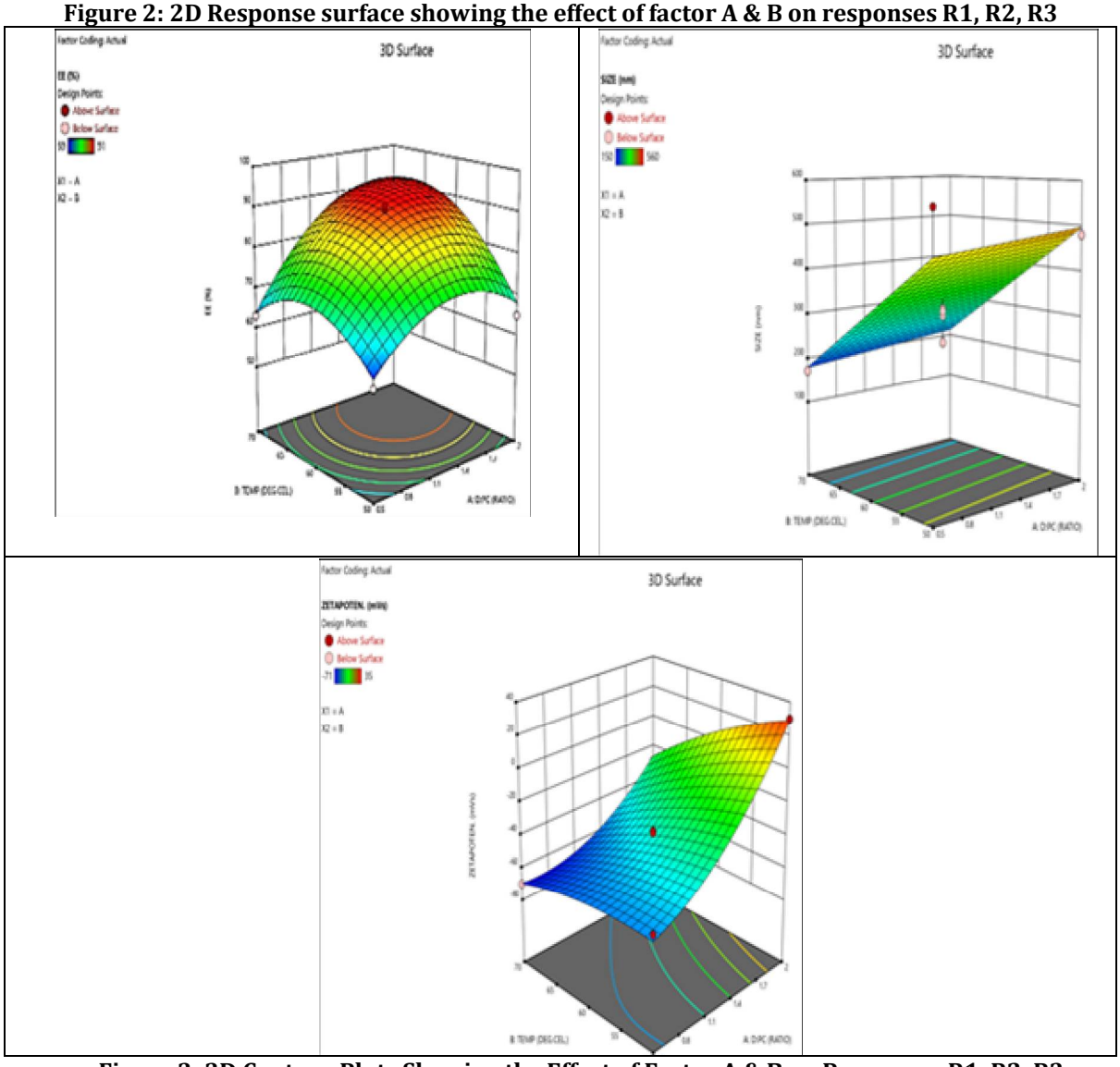


Figure 3: 3D Contour Plots Showing the Effect of Factor A & B on Responses R1, R2, R3

The 3D surface plots further explain the relationship between the variables and responses. Figure 3 presents the effect of drug: polymer ratio and temperature on particle size, entrapment efficiency, and zeta potential. The optimum particle size was obtained at a decreased drug: polymer ratio. Maximum Zeta potential and entrapment efficiency are based increase in drug: polymer ratio (table 3) [19].

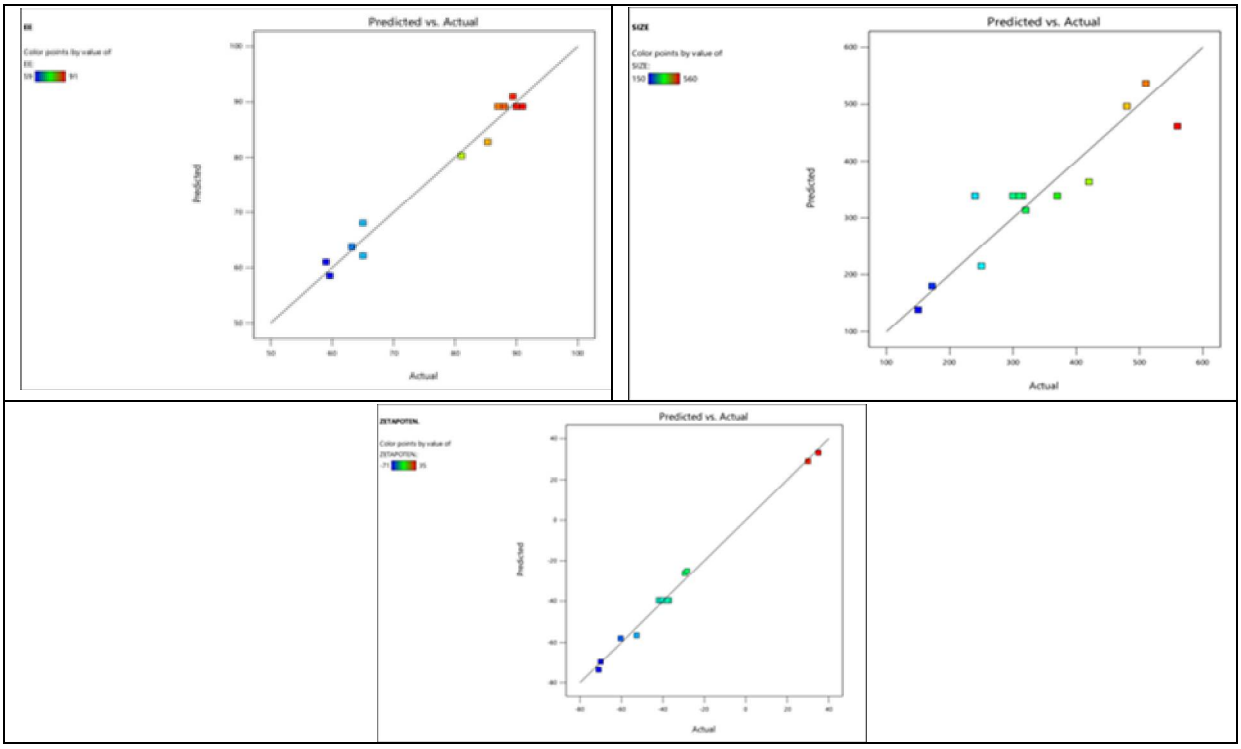


Figure 4: Linear correlation plots between predicted and actual values of responses

Table 2: Output data of regression analysis of 2 level 2 factor CCD of resveratrol Phytosomes

Responses	Model	R^2	Adjusted R^2	Predicted R^2	Adequate Precision	P Value
Y1 Entrapment Efficiency (%)	Quadratic	0.9793	0.9645	0.8813	19.2123	< 0.0001
Y2 Particle Size (nm)	Linear	0.8481	0.8177	0.7379	15.4362	< 0.0001
Y3 Zeta Potential (mV)	Quadratic	0.9946	0.9908	0.9694	50.2910	< 0.0001

Table 3: Effect of Variables on Responses

Sr. No	Factors	Effect	Response		
			Y1 (EE)	Y2 (PS)	Y3 (ZP)
1	Factor X1 (Drug:PC Ratio)	Increases	Increases	Increases	Decreases
2	Factor X2 (Temperature)	Increases	Decreases	Decreases	Increases

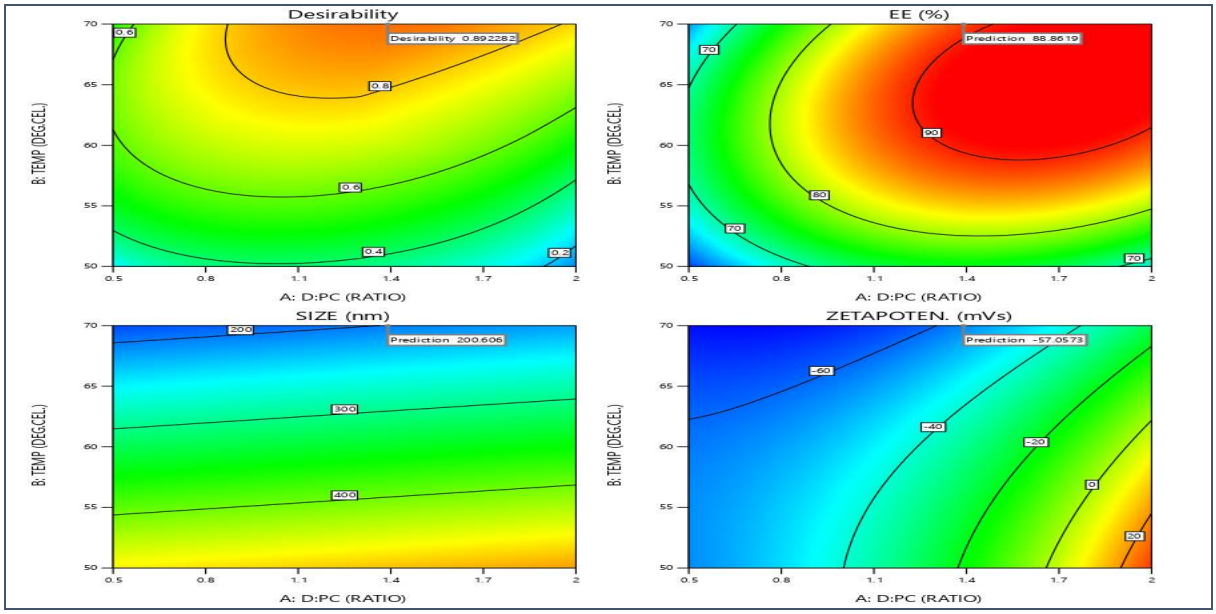


Figure 5: Response surface plot showing desirability for optimization

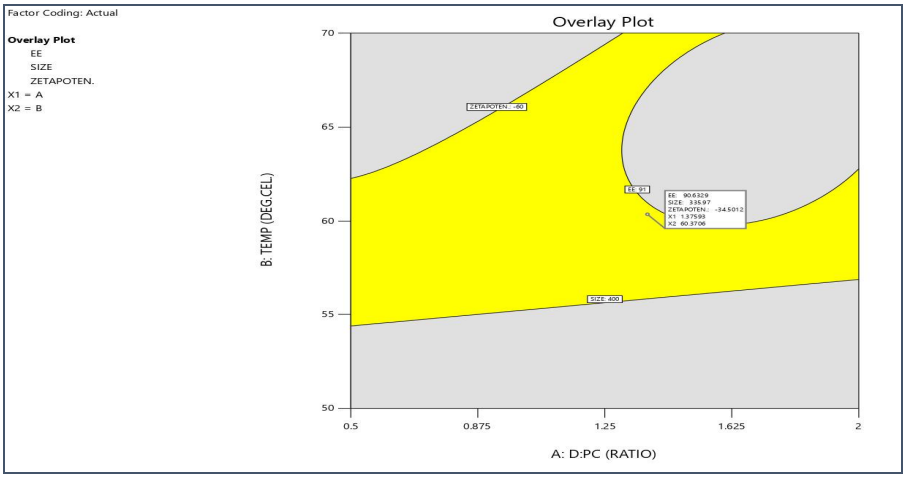


Figure 6: Overlay plot proposed by the design expert showing design space in yellow colour with composition of selected formulation with the responses

Table 4: Observed and predicted results of optimized Phytosomes

Sr. No	Responses	Predicted Values	Observed Values	% Relative Error
1	Entrapment Efficiency (%)	90.63	89.71	0.92
2	Particle Size(nm)	335.97	334.87	1.1
3	Zeta Potential(mV)	-34.50	-34.8	-0.3

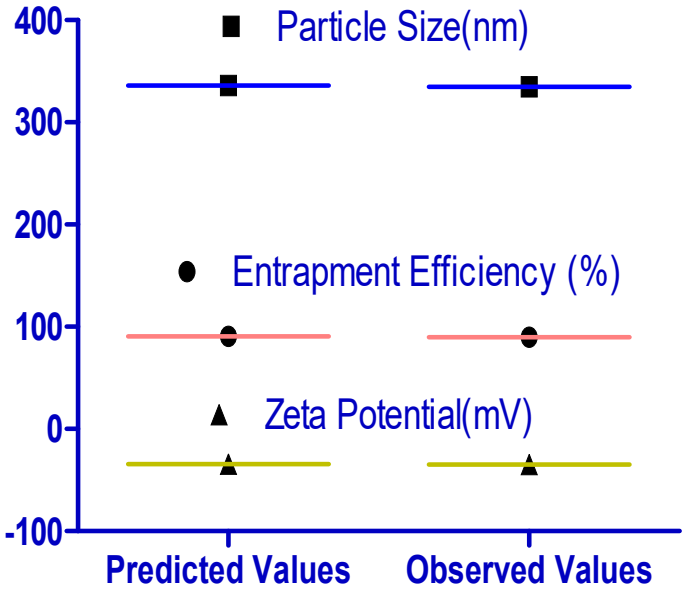


Figure 7: Observed and predicted results of optimized Resveratrol Phytosomes

Experimental batches prepared with the optimum values yield results within the predicted limits, thus confirming the reliability of the optimization process (Figure 7 and Table 4). When the observed results are compared with the predicted values, it is found that the prediction error varies between -0.3%, 1.1%which was very low, indicating that the optimization of phytosome by employing CCD would be a significant design to formulate a good and stable phytosome [20]. The results of the particle size distribution and zeta potential are shown in Figures 8 and 9.

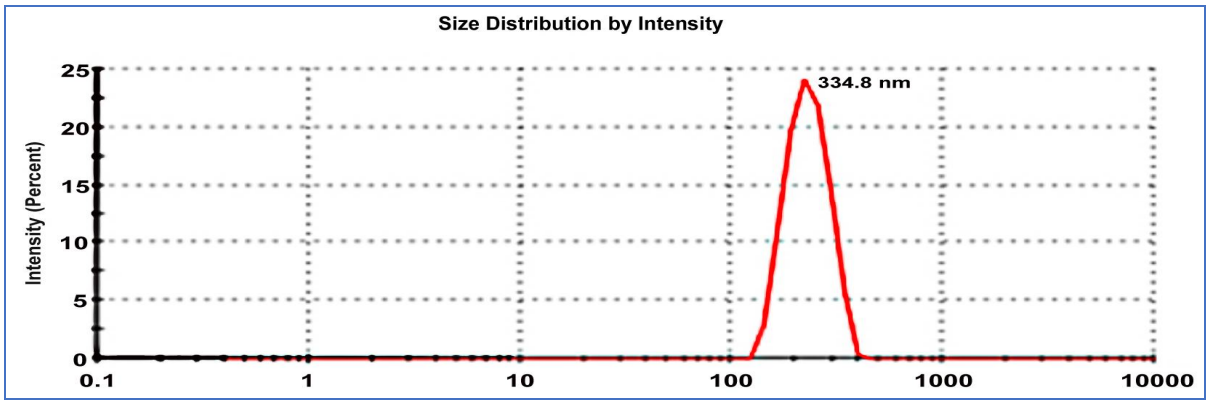


Figure 8: Particle size of optimized Phytosome

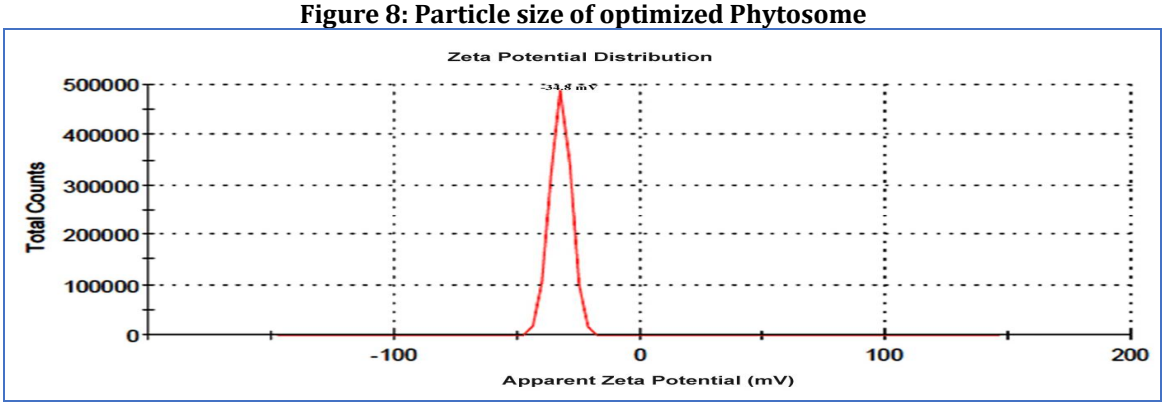


Figure 9: Zeta potential of optimized formulation

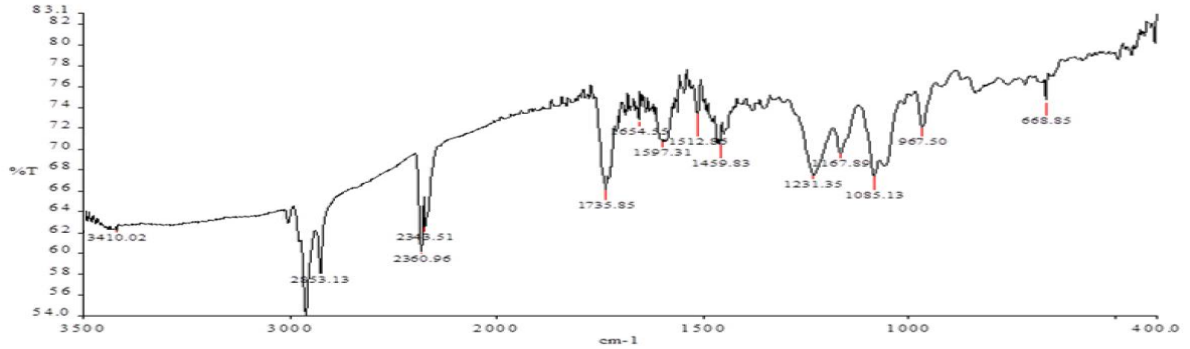


Figure 10: FTIR Spectrum of Optimized Resveratrol Phytosome

Infra-red spectra of the complex formed showed remarkable shifting of P-O-C and P=O absorption band of phospholipon from 1089.10 cm-1 to 1085.13 cm^{-1} and from 1240.57 cm-1 to 1231.35 cm-1, respectively, indicating interference at the polar head of the Phospholipon 90G . Furthermore, O-H stretching at 3293 cm^{-1} shows a narrow band in resveratrol IR spectra, while IR spectra of the resveratrol-phospholipid complex showed broadening and shifting of this band (Silverstein et al., 2005). Unlike intramolecular hydrogen bonding, where peaks are sharp and well defined, the spectrum of the complex gives broad bands indicating intermolecular hydrogen bonding between Phospholipon 90G and resveratrol, thereby confirming the complexation (Figure 10).

PREPARATION OF NANOPHYTOSOMES

Lipid hydration technique

The weighed amount of phospholipid was dissolved in organic solvent and dissolve it to get an organic phase. To this phase required quantity of herbal extract was dispersed uniformly to get a homogenous mixture. The homogenous mixture was taken into the round bottom flask which was fitted to the Rotary flash evaporator. A thin film was formed with the help of rotary flash evaporator based on condensation mechanism. The hydration of thin flim leads to formation of Phytosome complex suspension. The phytosomes are isolated from the suspension by precipitation with non-solvent. The collected phytosomes are dryed by Lyophilization process (Figure 11) [21].

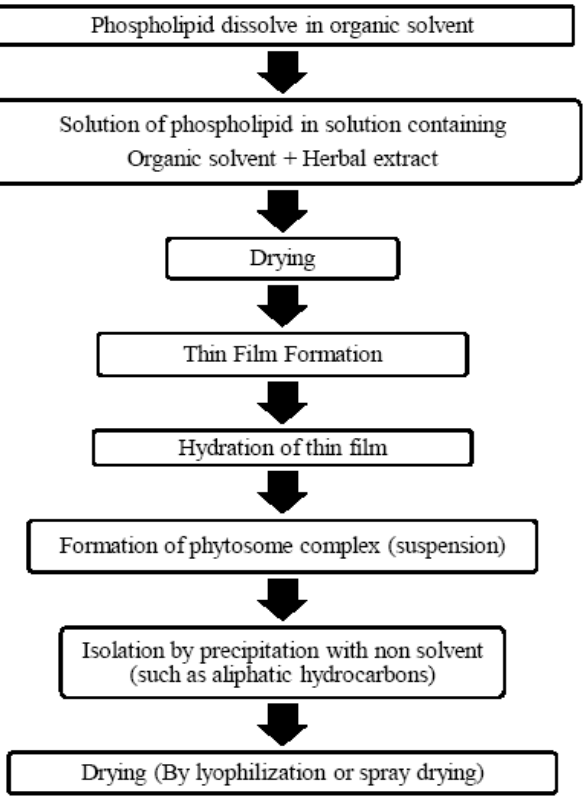


Figure 11: Lipid Hydration Technique

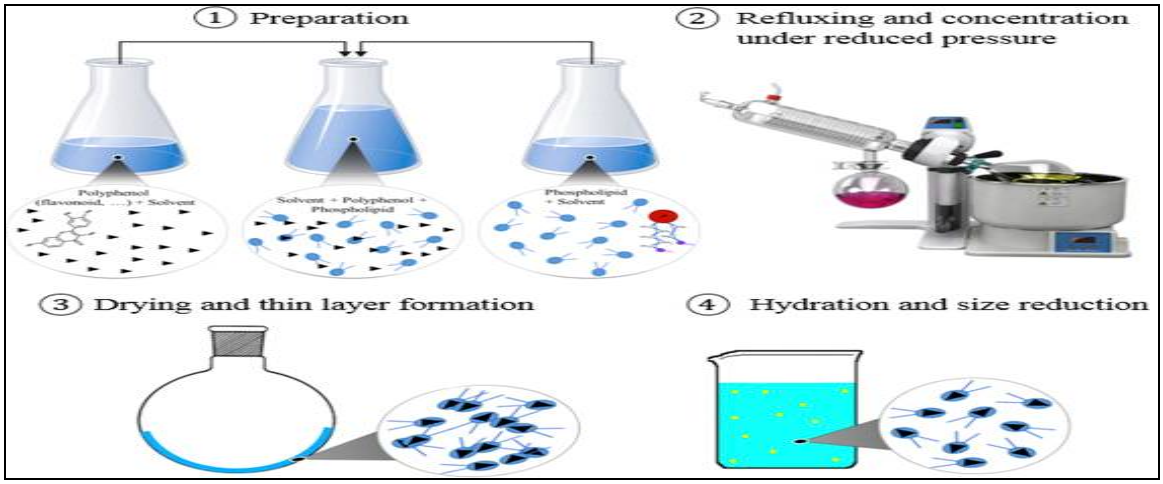


Figure 12: Solvent Evaporation Technique

RSVPs were prepared in different ratios of RSV to PC as per Central composite design. RSV was dissolved in methanol in a 200 ml beaker. In a 500 ml round-bottomed flask PC was dissolved in dichloromethane, and RSV solution was mixed. The mixture was refluxed for 2 hours at different temperatures. After 3 hours, the mixture was cooled and then poured to a petri dish. The dish was kept open overnight at room temperature for evaporation of solvent. Then the product was kept in hot air oven at 60°C for 2 hours. The dried product was stored in desiccators for further use (Figure 12) [22].

Preformulation Studies

Solubility Studies

Solubility studies were performed by taking an excess of the sample resveratrol in various solvents viz. water, ethanol, DMSO by bottle shaking method. The order of solubility of Resveratrol was found to be Ethanol > Dimethyl Sulfoxide (DMSO) > Water. From the data (Table 5) it was inferred that the Resveratrol shows good solubility in Ethanol, DMSO and Phosphate Buffer (pH 6.8) + PEG 400 (1:1) [23-25].

Table 5: Solubility studies of Resveratrol in various solvents

Water	Ethanol	DMSO	Phosphate Buffer (pH 6.8)	Acetate Buffer (pH 4.5)	Phosphate Buffer (pH 6.8) + PEG 400 (1:1)
0.08 ± 0.06	0.78 ± 0.08	0.67±0.12	0.102 ± 0.11	0.052 ± 0.01	0.4228 ± 0.24

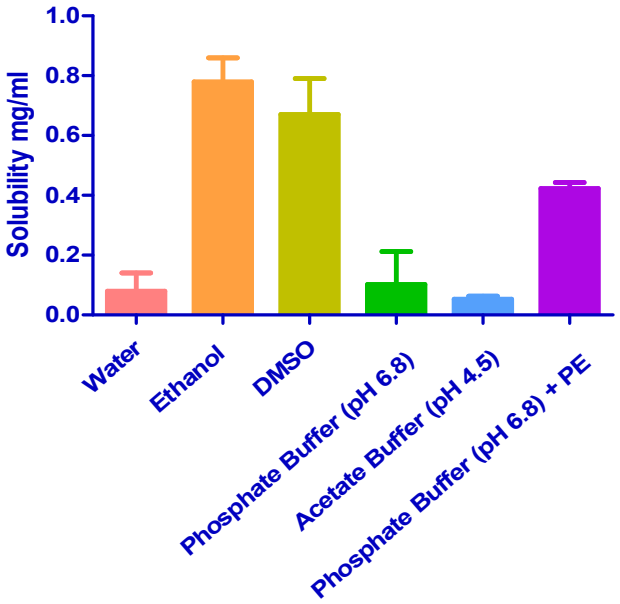


Figure 13: Solubility of Resveratrol in various solvents

Melting point by capillary method

The melting point of resveratrol is measured with the melting point apparatus, and the same was shown in Table 6. From the data, it was observed that the resveratrol melting point is within the acceptable criteria limits [26].

Table 6: Melting point of drugs

Drug	Melting point (^{0}C)	Acceptance criteria (^{0}C)
Resveratrol	257	***254***

Compatibility Studies

Resveratrol and excipients (Phospholipid) compatibility studies were carried out by FTIR (Figures 14,15,16 & 17) and DSC studies (Figures XX). The results show the drug and excipients used in the formulations were found to be compatible with each other.

FT-IR Studies

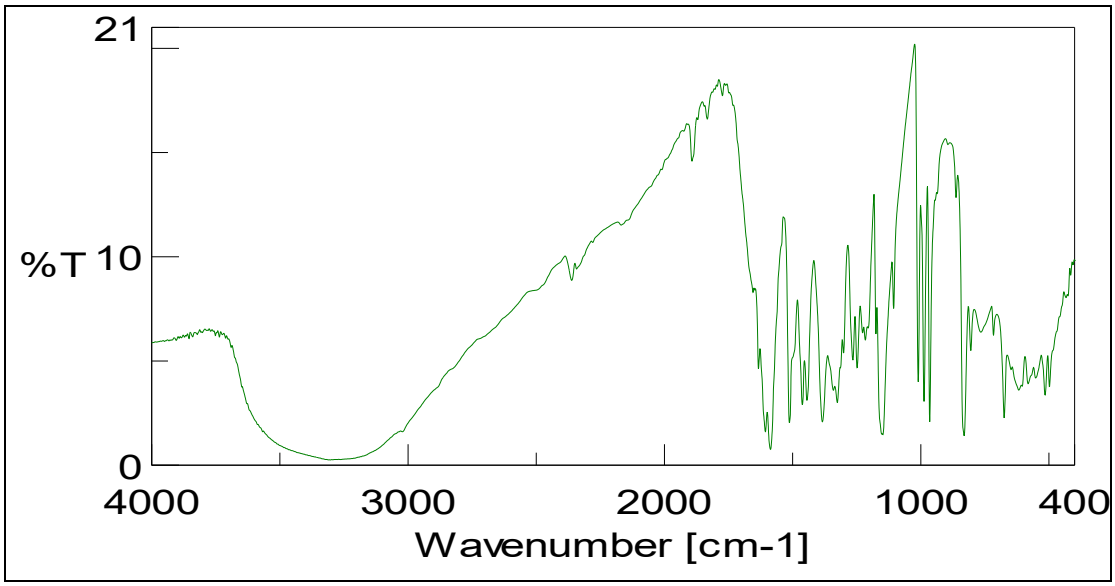


Figure 14: FTIR spectrum of Resveratrol Standard

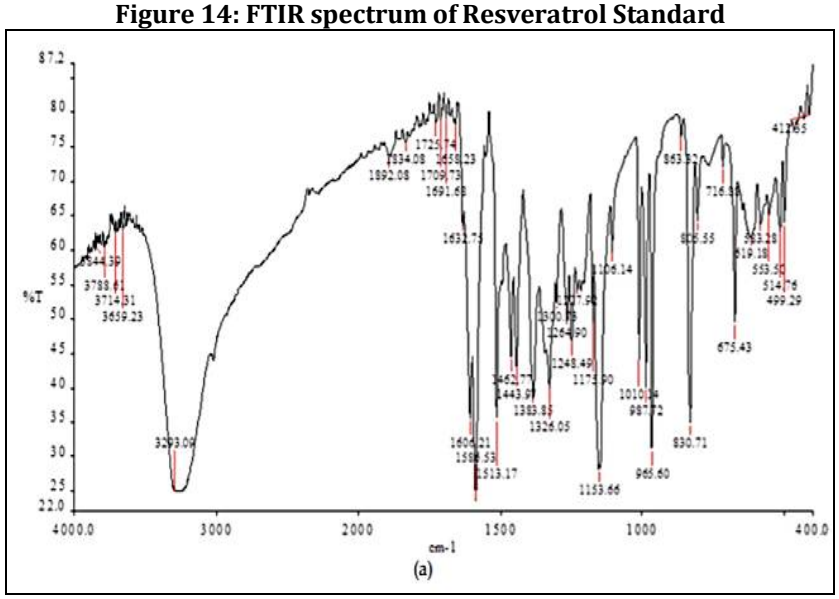


Figure 15: FTIR spectrum of Resveratrol extracted

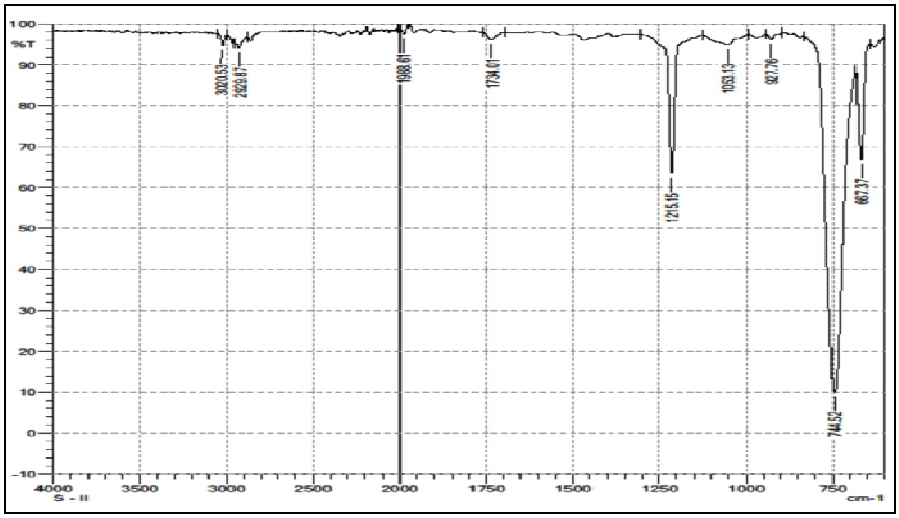


Figure 16: FTIR spectrum of Phosphadityl-choline with Cholesterol

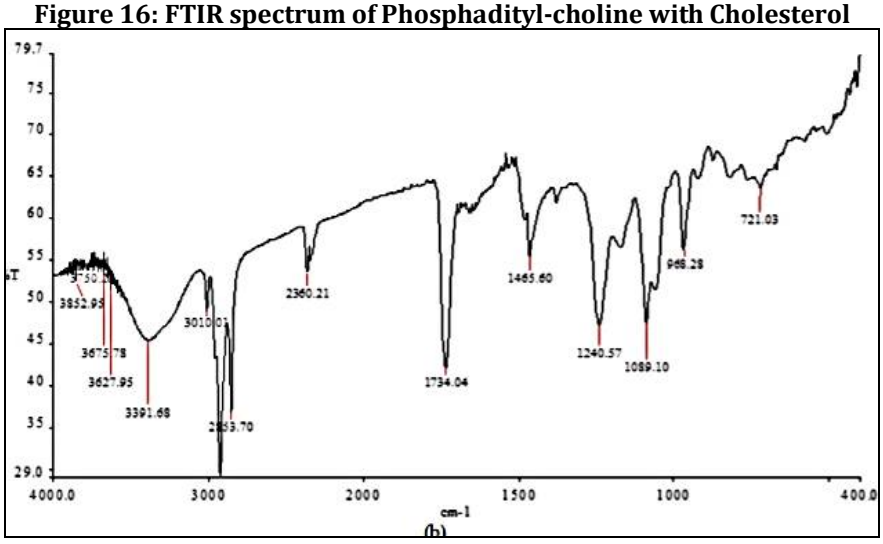


Figure 17: FTIR spectrum of Resveratrol extracted Phosphadityl-choline

Infra-red spectrum of resveratrol showed a typical trans olefinic band at 965.6 cm-1 and a narrow band of O-H stretching at 3293 cm^{-1}. Three characteristic intense bands at 1383.85, 1586.53 and 1606.21 cm^{-1} correspond to C–O stretching, C–C olefinic stretching, and C–C aromatic double-bond stretching. On the other side, the infrared spectrum of phospholipid showed O-H stretching at 3391 cm^{-1} and characteristic P=O stretching band at 1218 cm^{-1} and P-O-C stretching band at 1089 $cm^{-1,}$ and $N(CH_3)_3$ stretching at 744 cm^{-1}. Regarding the standard IR, the sample procured has similarities with the band ranges in Resveratrol and PC. Thus, from the FTIR studies it was inferred that the main functional group as in Resveratrol standard and extracted resveratrol, was found to be reproducible. It confirms that the extract has polyphenol i.e., resveratrol, which is responsible for anti-obesity activity [27-29]. The main functional group of resveratrol was found to be reproducible in the physical mixture, i.e. Resveratrol and phospholipid, which is used for the preparation of phytosomes. From the data, it was confirmed that the resveratrol and phospholipids are compatible with each other, and the selected phospholipid was suitable for the formulation of phytosome [30].

DSC Studies

DSC analysis for pure drug and lipids (phosphatidyl choline) was performed (Figure 18) and reported to determine the compatibility of the drug and excipients to formulate phytosomes. It is also used to determine the polymeric effect of encapsulated particles [31,32].

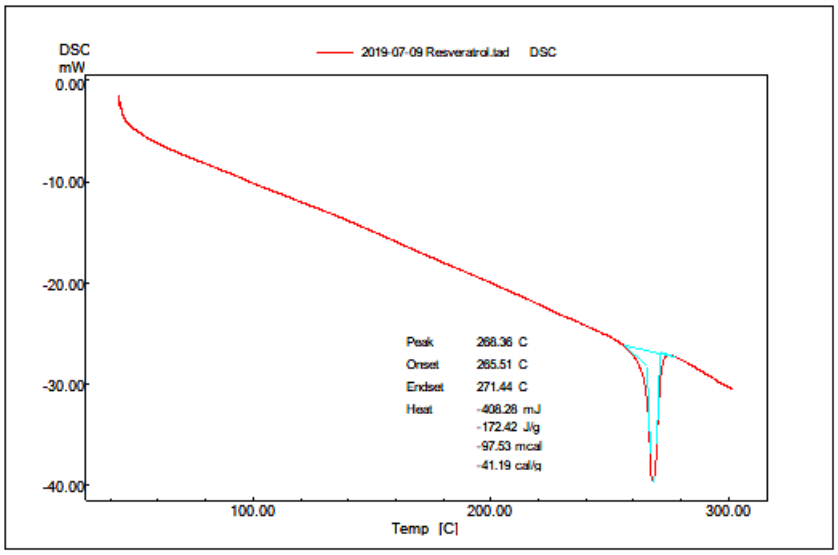


Figure 18: DSC curve of Phosphotidyl Choline

CONCLUSION

Resveratrol loaded nanophytosomes were prepared by using phosphatidylcholine (PC) and cholesterol by Lipid Hydration Technique, and optimization was done by response surface methodology. The physicochemical properties of prepared nanophytosomes were evaluated using particle size analyses, zeta potential, Fourier transformation infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC). Results showed that formulation with the Resveratrol: PC molar ratio of 1:2 possess the lowest particle size and the incorporation of cholesterol improved the physical stability of nanophytosome for over three weeks. FTIR and DSC analysis showed the formation of Resveratrol-phospholipid complex during the formulation development process.

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