Advances in Bioresearch
Adv. Biores., Vol 16 (6) November 2025: 67-78
©2025 Society of Education, India
Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.16.6.6778

Advances in Bioresearch

ORIGINAL ARTICLE

Formulation and Optimization of Phytosomes of Rutin

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ABSTRACT
Phytosomes represent a cutting-edge drug delivery system designed to enhance the bioavailability and therapeutic efficacy of plant-derived bioactive compounds such as flavonoids, alkaloids, polyphenols, and terpenoids. These compounds, despite their significant pharmacological activities (e.g., antioxidant, anti-inflammatory, hepatoprotective, and anticancer properties), often face challenges like poor solubility, limited permeability, and rapid metabolism. Phytosome technology addresses these limitations by forming molecular complexes between phytoconstituents and phospholipids, resulting in vesicular structures that improve absorption and systemic availability. This study aimed to develop and optimize rutin phytosomes to enhance the solubility, bioavailability, antioxidant, and hepatoprotective properties of rutin. The formulation employed a lyophilization method using a factorial design approach to optimize parameters such as the rutin-to-phospholipid (SPC) ratio and mannitol concentration. The optimized formulation showed a particle size of 287.09 nm, a drug content of 90.39% w/w, and a zeta potential of -28.2 ± 0.10 mV. DSC and FTIR confirmed the successful formation of the rutin-SPC complex. In vitro studies demonstrated enhanced solubility, controlled release, and stability under simulated gastric and intestinal conditions, with drug release following a Korsmeyer-Peppas model and achieving 90% release over 12 hours. In vivo evaluations highlighted improved hepatoprotective and antioxidant activities, with rutin phytosomes effectively mitigating paracetamol-induced liver damage. Pharmacokinetic analysis revealed superior bioavailability (C_max of 1.12 µg/mL and t_1/2 of 12.5 hours) compared to pure rutin (C_max of 0.48 µg/mL and t_1/2 of 4.2 hours).
Keywords: *Phytosomes, Rutin, Hepatoprotective, Antioxidant, Phospholipids, Solubility enhancement, Controlled release.*

Received 24.09.2025 Revised 23.10.2025 Accepted 19.11.2025

How to cite this article:
Mahajan Shraddha and Parihar Ashish. Formulation And Optimization of Phytosomes of Rutin. Adv. Biores. Vol 16[6] November 2025. 67-78

INTRODUCTION

Phytosomes represent a cutting-edge advancement in the field of drug delivery systems, specifically tailored to enhance the therapeutic efficacy of phytoconstituents derived from medicinal plants. Plant-derived bioactive compounds, such as flavonoids, alkaloids, polyphenols, and terpenoids, have long been recognized for their potent pharmacological activities, including antioxidant, anti-inflammatory, hepatoprotective, and anticancer properties. Despite their vast potential, these compounds often face challenges like poor water solubility, limited permeability, low bioavailability, and rapid metabolic degradation, which hinder their clinical applications. To overcome these barriers, the phytosome technology has emerged as a promising solution, offering a significant improvement in the delivery and bioavailability of these compounds [1-2]. Phytosomes are unique molecular complexes formed by the interaction of phytoconstituents with phospholipids, typically phosphatidylcholine, in a defined stoichiometric ratio. This interaction results in the formation of vesicular structures that are compatible with both hydrophilic and lipophilic environments. By mimicking the natural phospholipid bilayer of cellular membranes, phytosomes enhance the absorption and systemic availability of phytoconstituents, making them more effective in therapeutic applications. The formulation of phytosomes involves several critical steps, including the selection of appropriate phytoconstituents, optimization of the drug-to-phospholipid ratio, and the choice of suitable solvents and preparation techniques. Common methods for the preparation of phytosomes include solvent evaporation, anti-solvent precipitation, and thin-film

hydration. The success of formulation depends on achieving a stable and uniform complex that maintains the integrity of the bioactive compound while ensuring compatibility with biological systems [3-4]. Characterization of phytosomes is an essential aspect of their development, as it provides insights into their physicochemical properties and stability. Key parameters evaluated during characterization include particle size, zeta potential, encapsulation efficiency, and drug release profile. Advanced analytical techniques such as Fourier-transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR) spectroscopy, differential scanning calorimetry (DSC), and scanning electron microscopy (SEM) are employed to study the structural, thermal, and morphological attributes of phytosomes. These evaluations help in determining the suitability of the formulation for pharmaceutical applications and in ensuring batch-to-batch consistency [5]. Phytosomes have demonstrated significant potential in various pharmacological domains. Their enhanced bioavailability has been shown to improve the therapeutic efficacy of phytoconstituents in preclinical and clinical studies. For example, silymarin phytosomes have been extensively studied for their hepatoprotective activity, while curcumin phytosomes have shown improved anti-inflammatory and anticancer effects. In addition, phytosomes have also been explored for their antioxidant, antimicrobial, and neuroprotective properties [6]. Pharmacological evaluation of phytosomes involves both in vitro and in vivo studies to assess their therapeutic potential. In vitro studies provide a preliminary understanding of their efficacy, mechanism of action, and stability under physiological conditions. In vivo studies, on the other hand, evaluate the pharmacokinetics, biodistribution, and therapeutic outcomes in animal models or humans. These evaluations are crucial for validating the advantages of phytosomes over conventional formulations and for establishing their clinical relevance. The development of phytosomes aligns with the growing interest in natural and plant-based therapies, which are increasingly being recognized for their safety, efficacy, and minimal side effects. By addressing the limitations associated with conventional drug delivery systems, phytosomes have opened new avenues for the utilization of phytoconstituents in modern medicine. Furthermore, their compatibility with diverse administration routes, including oral, topical, and parenteral, enhances their versatility in therapeutic applications [7-9].

MATERIAL AND METHODS

Formulation of Rutin Phytosomes and Optimization

Formulation of rutin phytosomes

Rutin phytosomes were formulated by lyophilization method as described by Freag MS *et al.,* with slight modifications. First, rutin and SPC were weighed accurately in 1:1, 1:2, and 1:3 molar ratios; rutin was dissolved in DMSO and SPC was dissolved in t-butyl alcohol. Then, the rutin solution was added to the SPC solution followed by 3 h stirring on a magnetic stirrer for the formation of phytosomal complex. The solution containing phytosomal complex was then isolated by lyophilization with the addition of mannitol as cryoprotectant in 0.5 to 1.5 % W/V concentration. Before lyophilization, the solution was sonicated for 3 min. This solution was filled in vials, and vials were frozen at –80 ºC by keeping in ultra-low temperature freezer for 4 h. These frozen vials then placed in a lyophilizer with condenser temperature of –70 ºC. Lyophilization was done at 40 mbar pressure, and a shelf temperature of –40 ºC for 24 h followed by secondary drying at 25 ºC for another 24 h. The dried rutin phytosomal complex product was removed from the freeze drier, and filled in an amber-coloured glass container, and placed in a desiccator over fused calcium chloride at room temperature (20±2 ºC) until further use.

Design of experiments (DoE)

Preliminary studies carried out to identify the main factors that influence the rutin phytosomal formulation. The factors identified were drug: phospholipid ratio (w:w), and mannitol concentration (% w/v). The quadratic response surface design represented by the second-order polynomial model was used to investigate the effect of these factors on dependent variables, i.e. particle size (nm), and drug content (% w/w) of rutin phytosomes, in the optimization experiments by using Design Expert® software. Response surface methodology (RSM) is a group of statistical and mathematical methods that helps to carry out a systematic analysis of the formulations by optimizing the numerical parameters that can influence the response surface. Using response surface methodology, existing relation between numerical parameters can be quantified at different levels with obtained response surfaces. The independent factors drug: phospholipid ratio (A- w:w), and mannitol concentration (B- % w/v) were selected at three different levels, low (-1), medium (0), and high (+1) for each factor resulting in a 3 level factorial randomized quadratic design with nine independent experimental trials. The implied model can be explained by following quadratic equation exhibiting coefficient effects, interactions, and polynomial terms.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 + \ldots \quad \textbf{(Eq. 1)}$$

Where, Y is a measured response associated with the factor level combination, b_0 is an intercept, b_1 to b_{22} are regression coefficients computed from the observed experimental values of Y, and X_1 and X_2 are the coded levels of independent variables. The experimental design and the actual values of the independent variables are given in Table2.3. The different formulation batches of rutin phytosomes generated in 3 level facorial randomized quadratic design were formulated by the procedure explained above, and evaluated for the response, i.e. particle size, and drug content. After the model generation, model validation, and identifying the main and interaction effects on the response (particle size and drug content) were subjected to numerical optimization to get optimized rutin phytosomes.

Table 1: Independent and dependent variables, with their coded levels and actual values

Factors	Coded levels and actual values		
	-1 (Low)	0 (Medium)	+1 (High)
Independent variables			
A = Rutin: SPC ratio (w:w)	1:1	1:2	1:3
B = Mannitol concentration (% w/v)	0.5	1.0	1.5
Dependent variables			
R1 = Particle Size (nm) (R1)			
R2 = Drug Content (% w/w) (R2)			

In vitro Evaluation of Optimized Rutin Phytosomes

Average particle size, particle size distribution (PDI) and zeta potential

The mean particle size (PS), and size distribution as polydispersity index (PDI) of all the rutin phytosome formulations generated by DoE software including the optimized rutin phytosomes were determined by dynamic light scattering (DLS) technique, and the zeta potential (ZP) of the optimized rutin phytosomes was measured by electrophoretic light scattering (ELS) technique using Malvern Zeta Nano Sizer at a settled scrambling point of 90º at 25±0.5 ºC. The samples were diluted with distilled water in 1:10 ratio and sonicated using probe sonicator before the measurement. Measurements were performed in triplicates, and the results are expressed as mean size ± SD.

Extent of rutin incorporation in rutin phytosomes (drug content)

The rutin amount in the phytosomes was estimated by the spectroscopic method described by Tan Q *et al.,* accurately weighed amount of rutin phytosomes (~10 mg of rutin added) was dispersed in 5 ml of chloroform. The complex and pure SPC dissolves in chloroform, and free, uncomplexed rutin precipitates out. The dispersion was then filtered using Whatman® filter paper (ashless, grade 41, Sigma Aldrich). The free rutin residue was dried, dissolved in methanol and diluted suitably. This was analyzed using UV-VIS spectrophotometer at λ_{max} 360 nm. Drug content (percentage incorporated drug) was determined for all the rutin phytosome formulations generated by DoE software, including the optimized rutin phytosomes. The percentage incorporated drug was calculated by the following equation,

$$\%\ Incorporated\ drug = \frac{W(Added\ drug) - W(Free\ drug)}{W(Added\ drug)} X\ 100$$

In vitro drug release

In vitro drug release from the optimized rutin phytosomes was determined using the dialysis method. The dialysis sacks were washed as per the instruction given by the manufacturer. After proper pre-treatment, one end of the sack was tied, and known amount (10 mg) of pure rutin, and optimized rutin phytosomes (~10 mg of rutin) were placed inside the sacks. The other end of the sack was tied, and suspended vertically into a beaker placed on a magnetic stirrer with hot plate, beaker was containing 500 ml of buffer solution of pH 1.2 initially for 2 h, then it was replaced by pH 7.4 phosphate buffer in order to mimic the pH of the stomach and distal part of the small intestine. The content of the beaker was stirred at 100 rpm at 37 °C. The samples were withdrawn (5 ml) from the dissolution medium at specific time intervals, and the apparatus was immediately replenished with the same quantity of fresh buffer medium to maintain the sink condition. Samples were filtered and analyzed by UV-VIS spectrophotometer at λ_{max} 360 nm after the required dilutions.

***In vitro* drug release kinetics:**
The data obtained from the *in vitro* drug release study was fitted to kinetics release models (zero order, first order, Higuchi, and Korsmeyer-Peppas model) to understand the mechanism of drug release from optimized rutin phytosomes. The most appropriate model was selected based on the goodness of fit test.
Higuchi model
This model is based on the following hypothesis,

i. Initial drug concentration at the matrix is higher than drug solubility.
ii. The drug diffusion takes place only in a single dimension.
iii. Drug particles are smaller than the system thickness.
iv. Matrix swelling and dissolution are negligible.
v. Drug diffusivity is constant.
vi. Perfect sink condition is always attained in the release environment.

Higuchi describes the drug release from insoluble matrix as square root of the time- dependent process based on Fickian diffusion,

$$Q = Kt_{1/2}$$

Where,
K = Constant reflecting the design variables of the system.
*The plot made: % Cumulative drug release Vs square root of time

Korsmeyer-Peppas model
Korsmeyer derived a simple relationship which describes the drug release from a polymer system. To find out the mechanism of drug release, first, 60 % drug release data were fitted in Korsmeyer-Peppas equation,

$$M_t / M = Kt^n$$

Where,

M_t/M = Fraction of drug released at time t. K = Rate constant.
n = Release exponent.

In this model, the value of 'n' characterizes the release mechanism of the drug. $n \leq 0.45$ corresponds to the Fickian diffusion mechanism, $0.45 < n < 0.89$ to non-Fickian transport, $n = 0.89$ to case II (relaxational) transport and $n > 0.89$ to super case II transport.
*The plot made: Log % cumulative drug release Vs log time.

In vitro stability: *In vitro* stability study was performed for the optimized rutin phytosomes in pH 1.2 simulated gastric fluid (SGF), and pH 7.4 simulated intestinal fluid (SIF) containing no enzymes. Optimized rutin phytosomes sample (1 mg) was added to 10 ml of SGF, and SIF separately, and incubated for 2 h, and 6 h, respectively. Samples were stirred at 50 rpm at 37 °C temperature using a magnetic stirrer with a hotplate. The samples were then subjected to PS, PDI, and ZP study. All the experiments were carried out in triplicates, and the results are expressed as mean size ± SD.
***In vitro* antioxidant activity:** The free radical scavenging activity of pure rutin, SPC, and optimized rutin phytosomes was measured, and compared with the activity of standard (Ascorbic acid) using a stable free radical DPPH (2,2-diphenyl-1-picrylhydrazyl) as per the method described by Jamuna *et al.,* with slight modifications. The 0.1 mM solution of DPPH in methanol was prepared, and from this, 1.55 ml was added to 3.5 ml methanolic solution of pure rutin, SPC, and optimized rutin phytosomes of different concentrations ranged from 10-50 µg/ml. The absorbance of the standard and the samples was measured at 517 nm using Elisa reader. The % DPPH scavenged was calculated using the following formula

$$\% \text{ Inhibition of DPPH} = \frac{\text{Absorption (control)} - \text{Absorption (sample)}}{\text{Absorption (control)}} \times 100$$

RESULTS AND DISCUSSION
Preformulation Studies on Rutin
Preliminary Studies
Preparation of rutin phytosomes: The rutin phytosomes prepared by solvent evaporation method, salting out method, and lyophilization method during the preliminary studies.

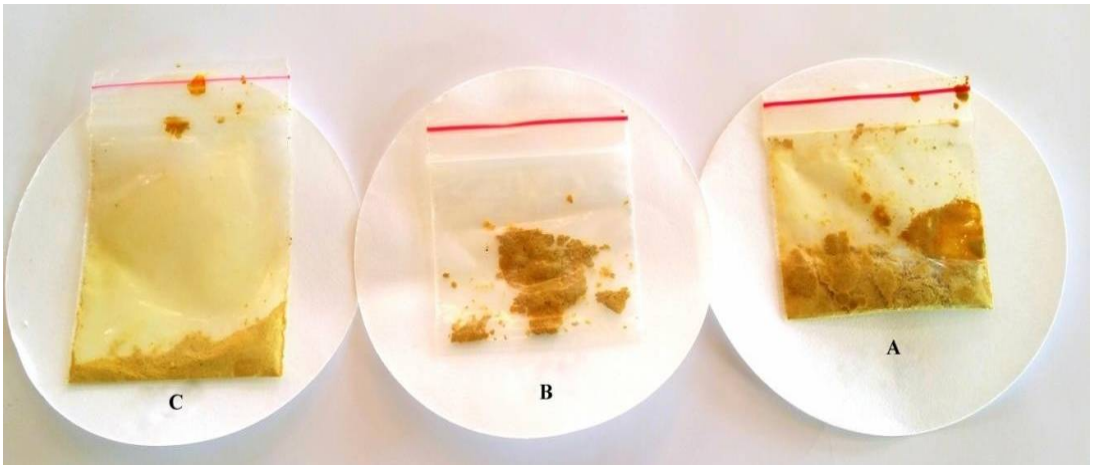

Figure 1: Photograph of phytosomal products obtained by solvent evaporation method (A),salting out method (B) and lyophilization method (C).

The phytosomal product obtained by the lyophilization method was found to be dry compared to the products obtained by the solvent evaporation method and the salting out method. Further, the prepared phytosomes were characterised by DSC and FTIR for the initial confirmation of the complexation between rutin and SPC.

Characterization of rutin phytosomes

Selection of formulation factors

From the visual observation, it was found that t-butyl alcohol and methanol were able to dissolve SPC without affecting the physical stability of the rutin in DMSO solution. Further, the soybean phosphatidylcholine 'Lipoid® S 100' had the best solubility in t-butylalcohol.

Formulation of Rutin Phytosomes and Optimization

Three level factorial design: On the basis of experimental design, the factor combinations have resulted in 9 different formulation batches of rutin phytosomes. The results obtained (particle size and drug content) for the experimental trials carried out using 3 level factorial randomized quadratic design with the obtained response particle size and drug content.

Table 2: Three level 71 factorial randomized quadratic design experimental trial batches,with obtained particle size (nm) and drug content (% w/w)

Std	Run	Factor 1	Factor 2	Response 1	Response 2
		A: RUTIN:SPC (w:w)	B: MANNITOL (% w/v)	Particle Size(nm)	Drug Content(% w/w)
4	1	-1	0	455.6	82.46
9	2	1	1	342.5	82.81
7	3	-1	1	488.2	79.93
3	4	1	-1	323.7	85.60
1	5	-1	-1	472.6	80.67
6	6	1	0	301.4	87.83
2	7	0	-1	286.7	90.16
8	8	0	1	298.5	88.37
5	9	0	0	274.2	93.24

Particle size (R1)

Model sum of squares: Quadratic model was suggested by the software.

Table 3: Sequential model sum of squares.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Mean vs Total	1.169E+06	1	1.169E+06			
Linear vs Mean	33925.98	2	16962.99	3.93	0.0811	
2FI vs Linear	2.56	1	2.56	0.0005	0.9831	
Quadratic vs 2FI	**25829.50**	**2**	**12914.75**	**563.87**	**0.0001**	**Suggested**
Cubic vs Quadratic	25.59	2	12.79	0.2967	0.7922	Aliased
Residual	43.12	1	43.12			
Total	1.229E+06	9	1.365E+05			

Model summary statistics

The predicted errors sum squares was found least, i.e. 632.74 in case of quadratic model.

Table 4: Model summary statistics.

Source	Std. Dev.	R^2	Adjusted R^2	Predicted R^2	PRESS	
Linear	65.70	0.5671	0.4228	0.0604	56210.35	
2FI	71.97	0.5671	0.3074	-1.0146	1.205E+05	
Quadratic	**4.79**	**0.9989**	**0.9969**	**0.9894**	**632.74**	**Suggested**
Cubic	6.57	0.9993	0.9942	0.8686	7858.82	Aliased

ANOVA for quadratic model

For the quadratic model, the F value and p value were found to be 521.82 and 0.0001,respectively and the model was found to be significant.

Table 5: ANOVA for response surface randomized 3 level factorial quadratic model forparticle size (nm).

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	59758.04	5	11951.61	521.82	0.0001	significant
A-RUTIN:SPC	33570.24	1	33570.24	1465.71	< 0.0001	
B-MANNITOL	355.74	1	355.74	15.53	0.0291	
AB	2.56	1	2.56	0.1118	0.7601	
A^2	24582.84	1	24582.84	1073.31	< 0.0001	
B^2	1246.67	1	1246.67	54.43	0.0051	
Residual	68.71	3	22.90			
Cor Total	59826.76	8				

Coefficients in terms of coded factors

The variance inflation factor (VIF) value was found to be 1 for all model terms.

Table 6: Coefficients in terms of coded factors.

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	269.82	1	3.57	258.47	281.17	
A-RUTIN:SPC	-74.80	1	1.95	-81.02	-68.58	1.0000
B-MANNITOL	7.70	1	1.95	1.48	13.92	1.0000
AB	0.8000	1	2.39	-6.82	8.42	1.0000
A^2	110.87	1	3.38	100.10	121.64	1.0000
B^2	24.97	1	3.38	14.20	35.74	1.0000

The generated equations for the response, i.e. particle size based upon thequadratic model

Final equation in terms of coded factors

$$\text{Particle Size} = +269.82 - 74.80 *A + 7.70*B + 0.8000*AB + 110.87*A^2 + 24.97*B^2$$

Final equation in terms of actual factors

$$\text{Particle Size} = +269.82222 - 74.80000*\text{RUTIN:SPC} + 7.70000*\text{MANNITOL} + 0.800000 *\text{RUTIN:SPC} *\text{MANNITOL} + 110.86667 *\text{RUTIN:SPC}^2 + 4.96667 *\text{MANNITOL}$$

Contour and 3D surface plots

The contour plot and the 3D surface plot for the response particle size respectively. From the plots it was analyzed that, the particle size decreased as the concentration of the rutin:SPC increased till certain level, further increase in the concentration increased the particle size. The effect of mannitol was found to be less significant on particle size.

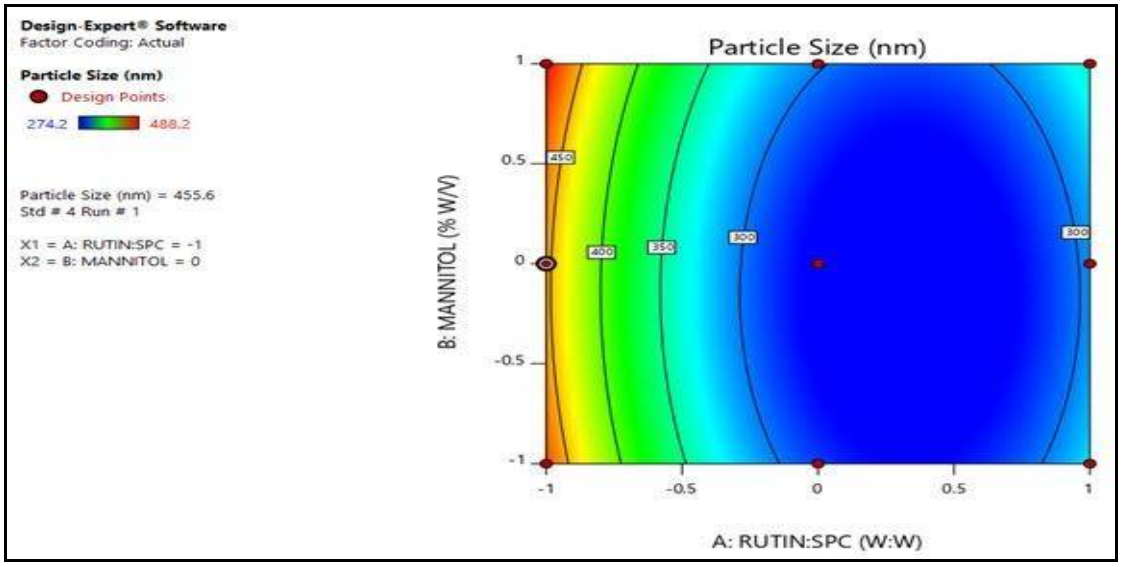

Figure 2: Contour plot of particle size (nm) against rutin:SPC ratio (w:w) and mannitol concentration (% w/v)

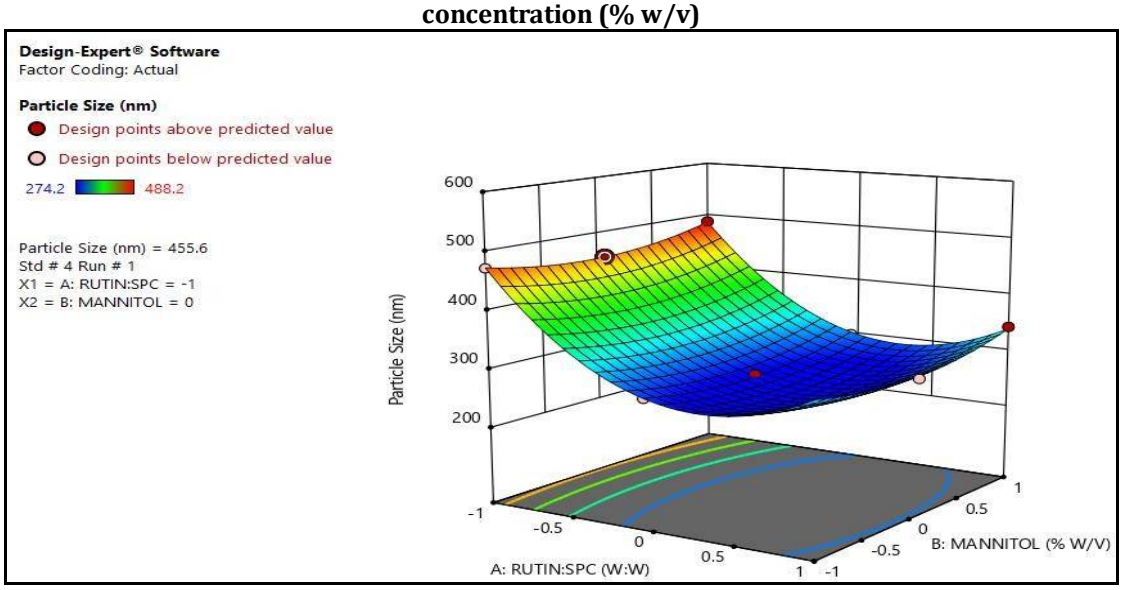

Figure 3: 3D surface plot of particle size (nm) against rutin:SPC ratio (w:w) and mannitol concentration (% w/v).

Drug content

Model sum of squares

Quadratic model was suggested by the software

Table 7: Sequential model sum of squares

Source	Sum of Squares	df	Mean Square	F-value	p- value	
Mean vs Total	66060.99	1	66060.99			
Linear vs Mean	33.67	2	16.83	0.7641	0.5063	
2FI vs Linear	1.05	1	1.05	0.0401	0.8493	
Quadratic vs 2FI	**129.90**	**2**	**64.95**	**157.59**	**0.0009**	**Suggested**
Cubic vs Quadratic	0.7156	2	0.3578	0.6870	0.6490	Aliased
Residual	0.5208	1	0.5208			
Total	66226.85	9	7358.54			

Model summary statistics

The predicted errors sum squares found least, i.e. 12.60 in case of quadratic model

Table 8: Model summary statistics.

Source	Std. Dev.	R^2	Adjusted R^2	Predicted R^2	PRESS	
Linear	4.69	0.2030	-0.0627	-0.6870	279.80	
2FI	5.12	0.2093	-0.2651	-2.7870	628.10	
Quadratic	**0.6420**	**0.9925**	**0.9801**	**0.9240**	**12.60**	**Suggested**
Cubic	0.7217	0.9969	0.9749	0.4277	94.92	Aliased

Model graphs for drug content

The main effects and interaction effects of factors with different levels on response are depicted in Figures. As the factor A changed from level -1 to 0 the drug content was increased and from 0 to +1 the drug content was decreased and from the factor level 0 to 0.5 the obtained drug content was between 90 to 95 %. The response drug content was not much affected by different levels of factor B. Least interaction effects were observed between two factors, i.e. A and B.

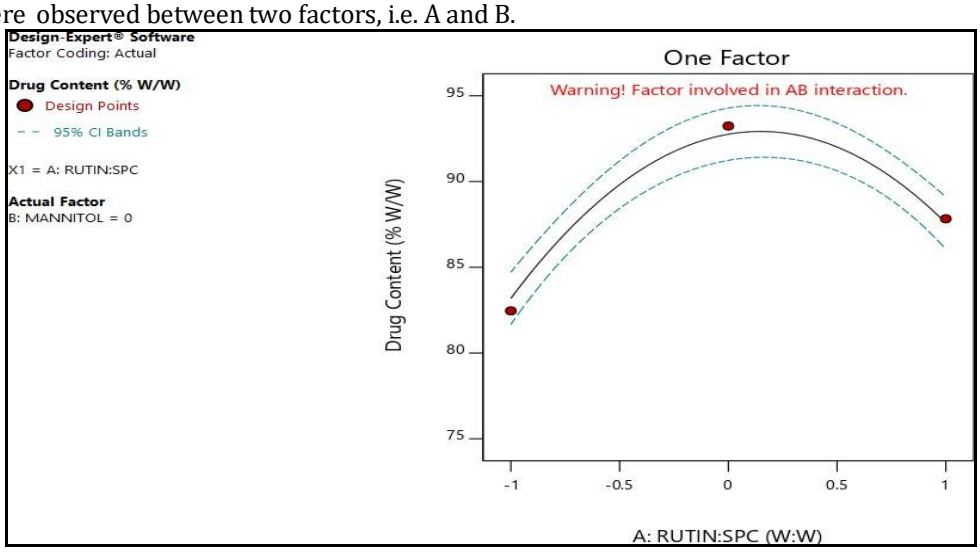

Figure 4: Main effects of factor A (rutin:SPC ratio) on response (drug content)

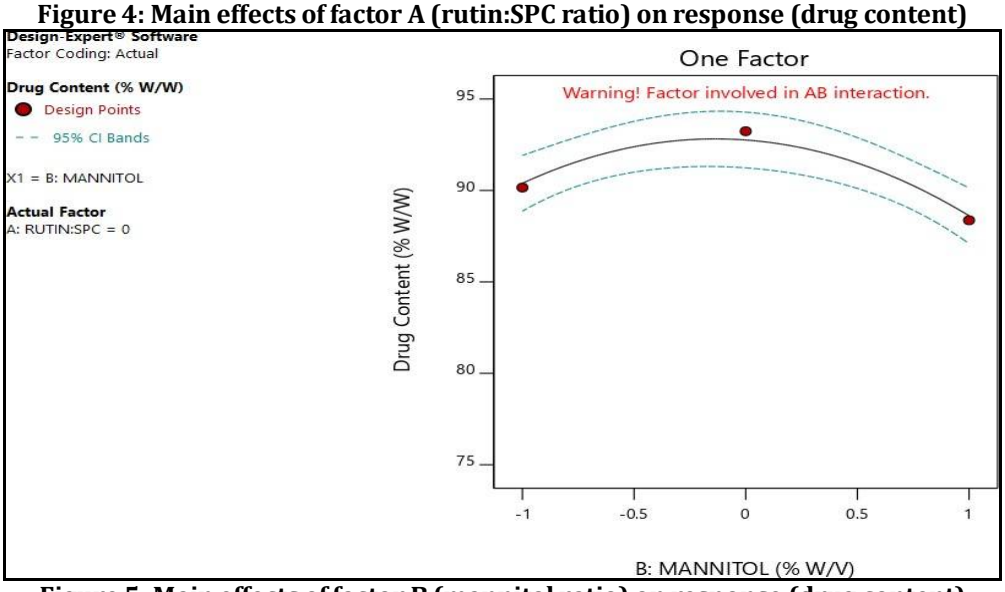

Figure 5: Main effects of factor B (mannitol ratio) on response (drug content)

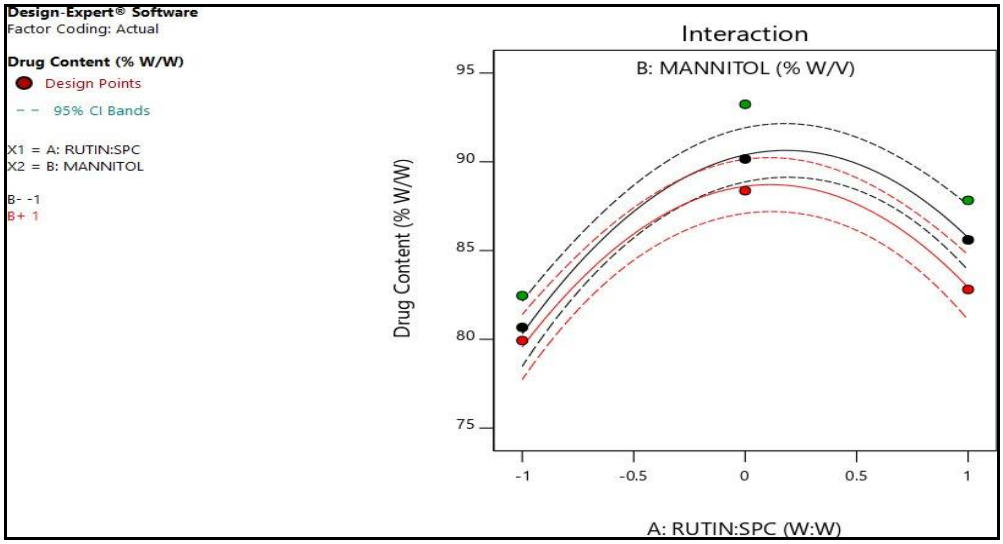

Figure 6: Interaction effects of factor A and B on response (drug content)

Predicted Vs Actual

The predicted and the actual values were found to be linear

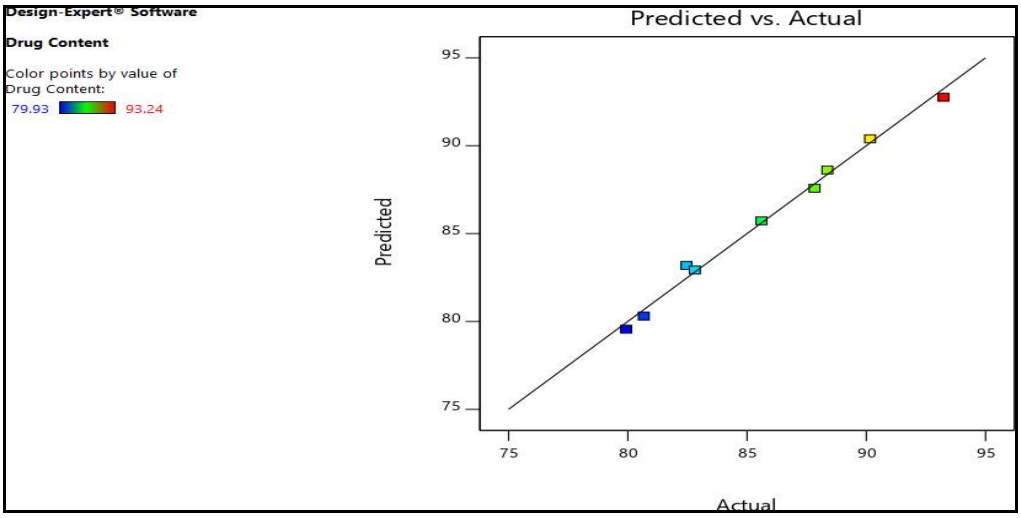

Figure 7: Predicted value and actual values of response (drug content)

Contour and 3D surface plots

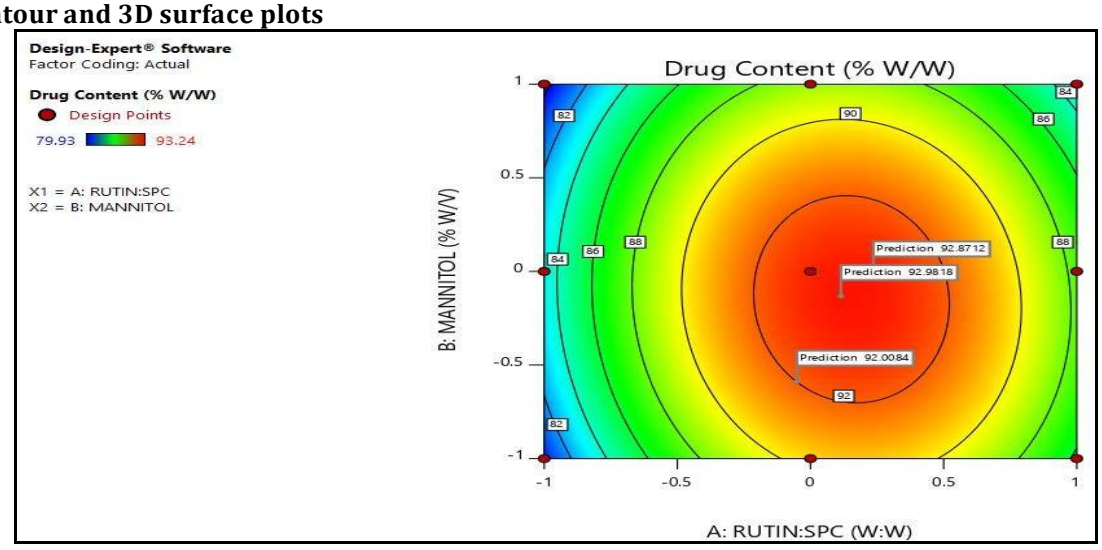

Figure 8: Contour plot of drug content (% w/w) against rutin:SPC ratio (w:w) andmannitol concentration (% w/v)

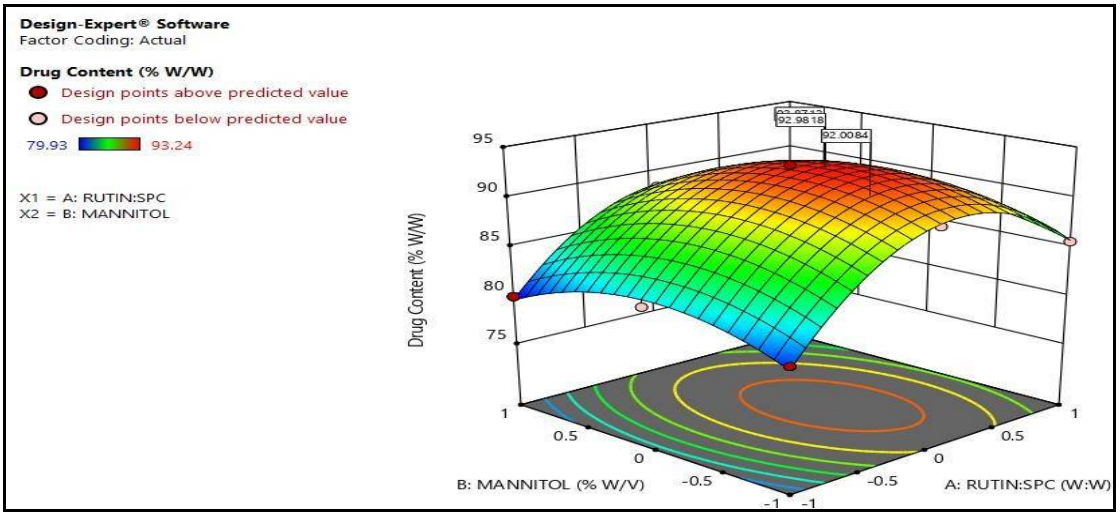

Figure 9: 3D surface plot of drug content (% w/w) against rutin:SPC ratio (w:w) andmannitol concentration (% w/v)

The contour plot and the 3D surface plot for the response drug content are given in Fig. respectively. From the plots it was analyzed that, the drug content increased as the concentration of the rutin: SPC increased till certain level, further increase in the concentration decreased the drug content. The effect of mannitol was found to be less significant on drug content.

Numerical optimization

For the factors A, B and response particle size, the goal was set 'in range', and for the response drug content, the goal was set to be 'maximize'. Minimum and maximum levels were provided for each parameter included. The different solutions (first six out of 92 solutions generated) given by the software using different combinations of independent levels along with desirability. The ramp picture showed that, for the selected solution, particle size and drug content predicted by the software was 287.089 nm and 90.3922 % w/w, respectively. The desirability was found to be 1 for the selected formulation. The perturbation plot showed the sensitivity of the factors rutin:SPC at level 0 and mannitol concentration at level -1. Interaction plot showed the interaction effect of two factors, i.e. rutin:SPC concentration and mannitol ratio indicated the resulted responses particle size and drug content is majorly affected by rutin:SPC concentration. The flagged desirability points on the 2D contour plot for desirability and the 3D desirability plot showed that the selected formulation with 1:2 rutin:SPC ratio and 0.5 % w/v mannitol concentration will possess the particle size 287.089 nm and drug content 90.392 % w/v.

Table 9: Constraints: A summary spreadsheet to show all of the criteria applied to findthe optimal settings.

Name	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
A:RUTIN:SPC	is in range	-1	1	1	1	3
B:MANNITOL	is in range	-1	1	1	1	3
Particle Size	is in range	280	350	1	1	3
Drug Content	maximize	80	90	1	1	3

Table 10: Solutions (first six) given by the software

Number	RUTIN:SPC	MANNITOL	Particle Size	Drug Content	Desirability	
1	**0.000**	**-1.000**	**287.089**	**90.392**	**1.000**	**Selected**
2	-0.256	-0.669	302.423	90.762	1.000	
3	-0.455	-0.142	326.304	90.258	1.000	
4	-0.353	-0.626	315.209	90.230	1.000	
5	0.168	0.764	280.956	90.276	1.000	
6	0.779	-0.438	280.000	89.932	0.993	

In vitro Evaluation of Optimized Rutin Phytosomes

Average particle size, particle size distribution (PDI) and zeta potential

The PS and ZP obtained for all the rutin phytosome formulations generated by DoE software. The PS, PDI, and ZP of optimized rutin phytosomes was found to be 272.6±2.48 nm, 0.376±0.02 and -28.2±0.10 mV, respectively.

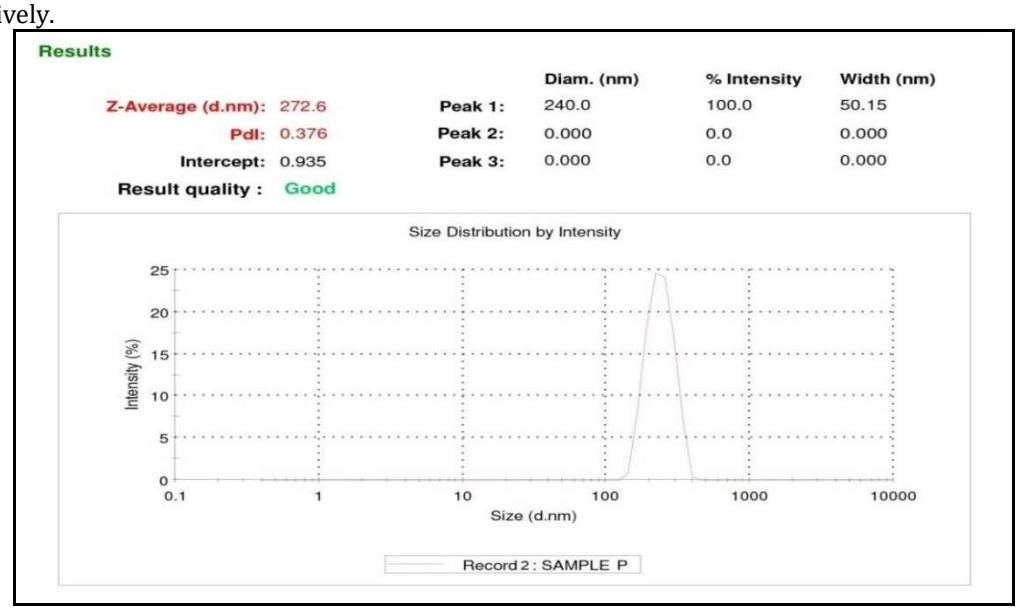

Figure 9: Average particle size and poly dispersity index of optimized rutin phytosomes

CONCLUSION

This dataset summarizes studies on phytosomes, focusing on pre-formulation and evaluation in polymeric nanoparticle formulations. The research aimed to develop and optimize rutin-loaded phytosomal nanocarriers, forming a nanovesicular pre-concentrate that converts into a liquid vesicular form in gastrointestinal media. The study targeted enhanced solubility, oral bioavailability, antioxidant, and hepatoprotective activities compared to pure rutin. Using a factorial design, key formulation factors, including co-solvent and phospholipid type, were optimized. Characterization confirmed successful complex formation, with in vitro studies demonstrating improved solubility, sustained drug release, and stability. In vivo evaluations revealed significant hepatoprotective and antioxidant effects, including mitigation of paracetamol-induced liver damage and restoration of enzyme levels. Pharmacokinetics showed enhanced bioavailability, prolonged serum concentration, and superior therapeutic outcomes, positioning rutin phytosomes as a promising platform for oral drug delivery.

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