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Design, Optimization, and Evaluation of Resveratrol Based Nanostructured Lipid Carriers for Enhanced Antidiabetic Efficacy

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ABSTRACT

Aim: To design, optimize and evaluate Resveratrol-loaded Nanostructured Lipid Carriers (NLCs) for improved drug delivery, controlled release, and enhanced therapeutic efficacy in the treatment of diabetes mellitus.

Objective: To overcome the limitations of conventional antidiabetic therapies by formulating optimized Resveratrol-loaded NLCs and evaluating their physicochemical properties, drug loading, entrapment efficiency, particle morphology (TEM), and in vitro release profile.

Method: Resveratrol-loaded NLCs were prepared by the high-speed homogenization method using varying concentrations of solid lipids, liquid lipids, and surfactants. The formulations were characterized for particle size, zeta potential, drug loading, and entrapment efficiency. FTIR and DSC analyses were performed to assess drug–excipient compatibility, while TEM was used to study particle morphology. In vitro release studies were conducted to evaluate controlled drug release behavior.

Result: FTIR and DSC studies confirmed the absence of drug–excipient incompatibility. The optimized formulation (RF4) showed a particle size of 196.2 nm, drug content of 95.21%, and entrapment efficiency of 95.38%. TEM images revealed smooth, spherical nanoparticles. The in vitro release profile indicated controlled drug release, and stability studies confirmed excellent physical stability under accelerated conditions.

Conclusion: Resveratrol-loaded NLCs demonstrated controlled release, high stability, and superior drug encapsulation, indicating strong potential as an effective and stable nanocarrier system for the management of diabetes mellitus.

KEYWORDS: Saw Palmetto, Beta-Sitosterol, Pygeum Africanum, Phytotherapy, Benign Prostatic Hyperplasia, BPH 2.

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INTRODUCTION[1,2,3,4]

Resveratrol, a naturally occurring polyphenol, has demonstrated significant antidiabetic and insulin-sensitizing properties in preclinical studies, and clinical investigations have reported modest improvements in glycemic control and insulin sensitivity in type 2 diabetic patients. However, its clinical application is severely constrained by extremely low oral bioavailability often less than 1% largely due to extensive first-pass metabolism in the intestine and liver. These limitations emphasize the need for advanced drug delivery strategies to enhance resveratrol's solubility, stability, and systemic absorption for effective oral therapy. Nanotechnology-based delivery systems have emerged as promising solutions to such challenges. In particular, Nanostructured Lipid Carriers (NLCs) have gained attention as oral delivery platforms for poorly water-soluble drugs. Composed of a blend of solid and liquid lipids stabilized by surfactants, NLCs form a submicron colloidal matrix, offering multiple benefits including improved solubility and stability, enhanced bioavailability, controlled drug release, and the potential for combination therapies.

MATERIALS AND METHOD

Materials

Resveratrol was purchased from Herbal Creative, Pvt. Ltd, New Delhi, India. Whereas excipients available in research centre were obtained from: glycerol monostearate from molychem, Mumbai, stearic acid from cosmochem, pune, castor oil from vikas Pharmaceuticals, oleic acid from labware chemicals, tween 20, 40,60 ,80 from oxford lab fine chem.

Methods

Preformulation studies[5,6,7]
Identification of drugs
Appearance:

The pure drugs Resveratrol were recognized by different organoleptic characteristics.

Melting point

The melting point of resveratrol was determined by placing a small quantity of the drug in a capillary tube, which was then affixed to the stem of a thermometer positioned at the center of a heating bath. The bath was gradually heated, and the temperatures corresponding to the onset and completion of melting were carefully recorded.

Solubility study of Resveratrol

The solubility of resveratrol was investigated using the shake flask method. The study was conducted in different solvent systems, including ethanol, distilled water, phosphate buffer (pH 7.4), phosphate buffer (pH 6.8), and acidic buffer (pH 1.2), to evaluate its solubility under various physiological and experimental conditions.

Spectrophotometric characterization of Resveratrol in UV Spectroscopy [8, 9].

a. Determination of Absorption Maxima i.e. λmax

A standard solution of resveratrol was scanned in the wavelength range of 200–400 nm using a UV–Visible spectrophotometer (Shimadzu 1800). The stock solution was prepared by dissolving 25 mg of resveratrol in 25 ml of ethanol to obtain a concentration of 1000 µg/ml. From this stock solution, 0.1 ml was further diluted to 10 ml with ethanol to prepare a working solution of 10 µg/ml.

b. Standard calibration curve of resveratrol by UV Spectroscopy.

- Calibration Curve of Resveratrol in ethanol Preparation of stock solution in ethanol:

The standard stock solution was prepared by dissolving 50 mg of the drug in 50 ml of ethanol to obtain a concentration of 1000 µg/ml. The solution was scanned in the wavelength range of 200–400 nm using a UV–Visible spectrophotometer, and it exhibited maximum absorbance at 304 nm.

Preparation of dilutions for the standard curve:

From the 1000 µg/ml stock solution, 10 ml was diluted to 100 ml standard solutions with concentrations of 2, 4, 6, 8, 10, and 12 ppm were prepared by diluting with 10 ml with ethanol. The absorbance of each solution was measured at 304 nm using ethanol as the blank, and a calibration curve was constructed by plotting absorbance versus concentration.

FTIR Spectroscopy[10,11]

FTIR spectroscopy was employed both to obtain structural information about the compound and to assess its purity. The infrared spectrum of the sample was recorded, and spectral analysis was performed accordingly. A dry sample of the drug was directly placed on the sample holder and analyzed using an FTIR spectrophotometer (Perkin Elmer). FTIR is a vital analytical technique for chemical identification and for studying possible interactions between the drug and excipients. The spectra of the pure drug were recorded over a scanning range of 400–4000 cm^{-1}.

DSC Thermogram[12]

Differential Scanning Calorimetry (DSC) was used to investigate the thermal behavior of resveratrol, providing valuable information for compound identification and characterization. Thermal analysis was performed on pure resveratrol powder as well as on its physical mixtures with nanostructured lipid carriers (NLCs). Approximately 5 mg of each sample was accurately weighed, placed in an aluminum crucible, and sealed with an aluminum lid using a sealing machine. The thermograms were recorded at a heating rate of 10°C/min under an inert nitrogen atmosphere flowing at 30 ml/min, with Al_2O_3 serving as the reference material.

XRD studies of pure drug[13]

The physical properties of resveratrol, both in its pure form and within the lipid matrix, were evaluated using X-ray diffraction (XRD). Patterns were recorded on a Siemens DIFFRAC plus 5000 powder diffractometer with a Cu source at 40 kV and 30 mA. Samples were scanned over a 2θ range of 10°–90° with a step size of 0.01° and a scan rate of 10°/min.

Screening of solid lipid, liquid lipid & surfactant[14]

Screening of solid lipid, liquid lipid & surfactant was carried out for selection of excipients. Emulsification capacity of various excipients was studied by taking different concentrations.

Preparation of resveratrol loaded Nanostructured lipid carrier (NLC)

Resveratrol loaded NLCs was prepared by using High-speed homogenizer followed by ultrasonication.

- Briefly, solid lipid, liquid lipids, and resveratrol were accurately weighed and dissolved in 10 ml of a mixed ethanol solvent in a water bath at 55 °C.
- The resulting mixture was added dropwise to aqueous phase containing surfactant solution and maintained tempreature at 70 °C. A pre-emulsion was formed through homogenization at 15,000 rpm, followed by ultrasonication for 30 minutes at 70 °C.
- To prevent lipid crystallization, the pre-emulsion was further ultrasonicated for an additional 15 minutes.
- The resulting oil-in-water (o/w) emulsion was then gradually cooled to room temperature under continuous stirring, allowing the lipids to recrystallize and form the nanostructured lipid carriers (NLCs).

Experimental design[15,16]

The response surface methodology (RSM) was employed to perform Quality by Design approach for constructing and investigating the polynomial models, using fewer experimental runs. Central composite Design comprising of 2-factors and 2-levels was employed to examine the quadratic response surfaces by assessing the effect of pre-defined independent variables on different response dependent variables Drug content, Entrapment efficiency (%) and Drug release (%), was coded as Y1, Y2 and Y3. Three independent variables namely Lipid conc (%), Surfactant conc (%) and Homogenization speed (C) were chosen. Each of the variables was varied at two different levels, known as high and low levels. All the finalized independent variables and the response variables are described in Table below. For designing and optimization of batches Design-Expert® version 10.0 was used.

Table 01: List of Independent and Dependent variables in Box–Behnken design

Independent variable	Low value (-1)	High value (+)	Dependent variables	Constraints
Lipid conc (%)	2	5	Drug content (%)	Minimize
Surfactant conc (%)	1	1.5	Entrapment Efficiency (%)	Maximize
Stirring Speed (rpm)	10000	15000	Drug release (%)	Minimize

Table 02: DOE suggested batches for Resveratrol

Formulation code	Resveratrol (mg)	Lipid Conc (%)	Solid lipid (gm)	Liquid lipid (gm)	Surfactant Tween 80 conc (%)	Homogenization (Rpm)
RF1	100	5	1.05	0.45	1.5	15000
RF2	100	2	0.42	0.18	1	10000
RF3	100	3.5	0.735	0.315	1.25	12500
RF 4	100	3.5	0.735	0.315	1	15000
RF 5	100	2	0.42	0.18	1.25	10000

Evaluation of Nanostructured lipid carriers[17,18,19,20]

Drug content

The total drug content in the formulation was determined by dissolving 1 ml of the prepared NLCs in 10 ml of ethanol. The concentration of resveratrol in each formulation was quantified spectrophotometrically by measuring the absorbance of the clear supernatant at its maximum wavelength of 304 nm. All experiments were performed in triplicate, using acetonitrile as the blank for UV absorbance measurements.

In Vitro release Study

The in vitro release of resveratrol from NLCs was assessed using the dialysis bag method at 37 °C with phosphate buffer (pH 6.8) as the medium. A 2 mL sample of the NLC formulation was placed in the dialysis membrane and immersed in 100 mL of buffer under stirring at 75 rpm. Aliquots of 5 mL were withdrawn at 1, 2, 3, 4, 5, 6, and 8 hours, analyzed at 304 nm, and replaced with fresh buffer to maintain sink conditions. All measurements were performed in triplicate.

Entrapment efficiency (%)

A volume of 4 ml of each drug-loaded sample was centrifuged for 30 min to separate the lipid and aqueous phase. The supernatant was then diluted with Acetonitrile spectrophotometer and analyse at 304 nm. The entrapment efficacy of NLC was calculated as follows:

$$\textbf{Entrapment efficiency}\ (\%) = \frac{\textbf{Total amount of drug added (mg)} - \textbf{Unentrapped drug (mg)}}{\textbf{Total amount of drug added (mg)}} \times 100$$

Particle size and Zeta potential

The 100µl of NLC formulations was taken and mixed with distilled water and sonication was kept for 30 min. The analysis was performed at a temperature of 25 +1 ℃. Same procedure repeated at zeta potential.

Characterization of NLCs[21,22,23]

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetric (DSC) measurements were carried out on a modulated DSC (Mettler Toledo, SW STARe, and USA). The optimized batch (RF4) were weighed (2-8mg), the aluminum pans were used and hermetically covered with lead. The heating rage was 50- 250 °C for sample with constant increasing rate of temperature at 10°C /min under nitrogen atmosphere (50-60ml/min). The resultant thermogram of formulation was obtained.

Stability Study[24,25]

Accelerated Stability Study

The optimized NLC of Resveratrol were packed and sealed in class 1 glass vials with a screw lid and was kept for stability studies in long term as well as in accelerated stability conditions as per international conference on harmonization ICH [Q1A(R2)] guidelines.

- Long term stability studies at 5° ± 3° C
- Accelerated stability studies at 25° ± 2° C / 60 % ± 5 % RH

RESULT AND DISCUSSION

Identification of drug Appearance
API:- Resveratrol

Organoleptic Characteristic of Resveratrol	
Parameter	**Description**
Appearance	White to off-white powder
Odor	Odorless or slightly characteristic
Taste	Tasteless or slightly bitter
Texture	Fine powder
Solubility	Poorly soluble in water; soluble in Ethanol, Methanol, DMSO, and PEG

Melting point

The melting point of resveratrol was determined using the capillary tube method. A sample was packed into a capillary tube, which was then tied to a thermometer and suspended in a Thiele's tube. The setup was heated until the drug sample completely melted.

Table 03: Melting point of Resveratrol

Drug	Standard value	Observed value
Resveratrol	261–263^{0}C	260^{0}C

Solubility study of Resveratrol

Table 04: Solubility study of Resveratrol

Sr.No.	Drug	Solvent	Solubility status
1	Resveratrol	Ethanol	Soluble
2	Resveratrol	Distilled water	Very poorly soluble
3	Resveratrol	Phosphate buffer pH 7.4	Extremely low solubility
4	Resveratrol	Phosphate buffer pH 6.8	Moderate solubility
5	Resveratrol	Phosphate buffer pH 1.2	Better solubility

Spectrophotometric characterization of Resveratrol in UV Spectroscopy.
Determination of Absorption Maxima i.e. λmax

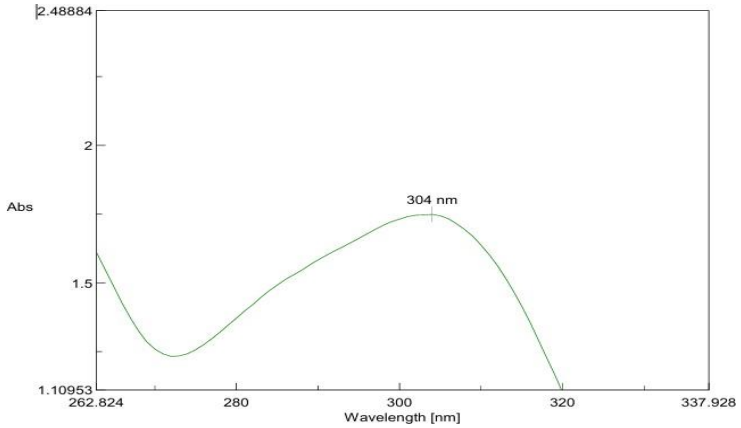

Figure 01: UV spectrum of Resveratrol in ethanol (10µg/ml)

Table 05: λmax of Resveratrol

Drug	λmax	Reported λmax
Resveratrol	304	306

Standard calibration curve of resveratrol by UV Spectroscopy.

- **Calibration Curve of Resveratrol in ethanol**

Table 06: Calibration Curve of Resveratrol in ethanol

Concentration (µg/ml)	Absorbance
0	0
2	0.0521
4	0.1019
6	0.1485
8	0.2067
10	0.2617
12	0.3041

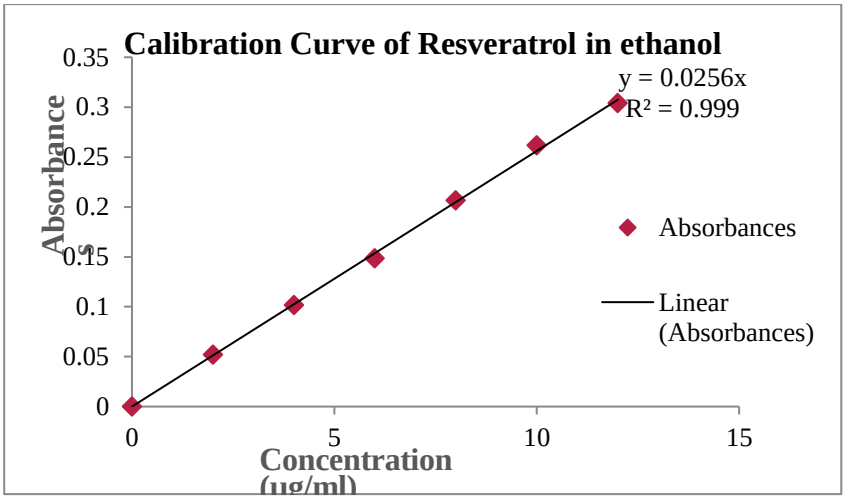

Figure 02: Calibration Curve of Resveratrol in ethanol

FTIR Spectroscopy

- **FTIR of Resveratrol**

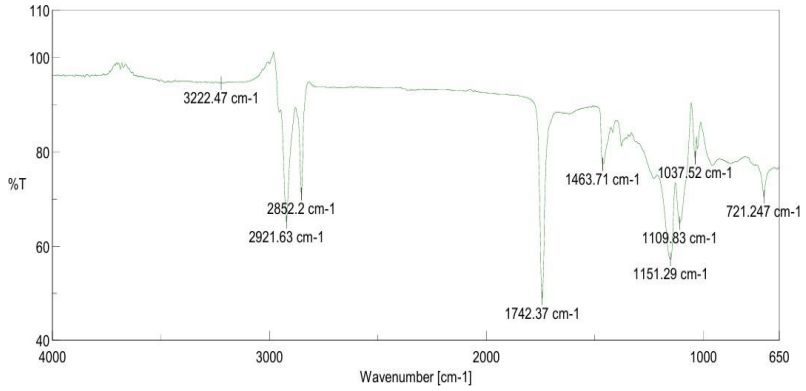

Figure 03: IR spectra of Resveratrol

Vibrational Mode	Wavenumber (cm^{-1})	Description
Phenolic O–H bond stretching	2852.20, 2921.63, 3222.47	Broad absorption bands due to stretching vibrations of phenolic hydroxyl groups
Aromatic C=C bond stretching	1742.37	Stretching vibration due to aromatic ring C=C bonds
Olefinic C=C bond stretching	1463.71, 1037.52	Stretching vibrations from trans-olefinic double bond
Aromatic C–H bending (out-of-plane)	721.25	Out-of-plane bending of aromatic C–H bonds

FTIR of Resveratrol NLC Physical mixture

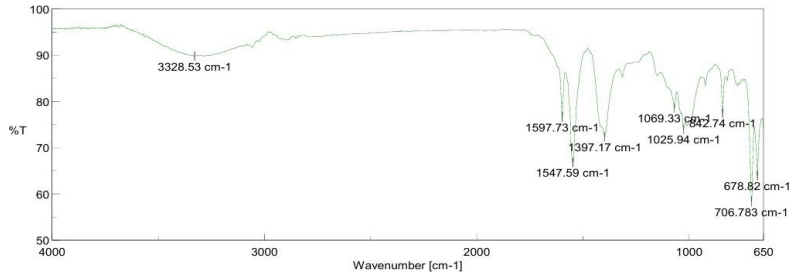

Figure 04: IR spectra of Resveratrol Physical mixture

Analyzing the FTIR spectra of the physical mixture of Resveratrol Nanostructured Lipid Carriers (NLC) is a crucial step in assessing potential interactions between the drug and the carrier components. The FTIR spectra show that there is no incompatibility between Resveratrol and the excipients. The peaks observed in the physical mixture correspond to the vibration frequencies of pure Resveratrol, indicating the absence of any significant interaction between the drug and the formulation components. The observation of FTIR are as follows

Vibrational Mode	Wavenumber (cm^{-1})	Description
Phenolic O–H bond stretching	3328.53	Broad absorption band due to stretching vibrations of phenolic hydroxyl groups
Aromatic C=C bond stretching	1597.73, 1547.59	Characteristic stretching vibrations from aromatic rings
Olefinic C=C stretching	1397.17, 1025.94	Stretching vibrations due to trans-olefinic double bonds
Aromatic C–H bending (out-of-plane)	706.78	Out-of-plane bending vibrations of aromatic C–H bonds

DSC Thermogram

DSC Thermogram Analysis

The DSC thermograms of resveratrol are shown below. Both the pure resveratrol and its physical mixture exhibited a melting endothermic peak at 268.53°C.

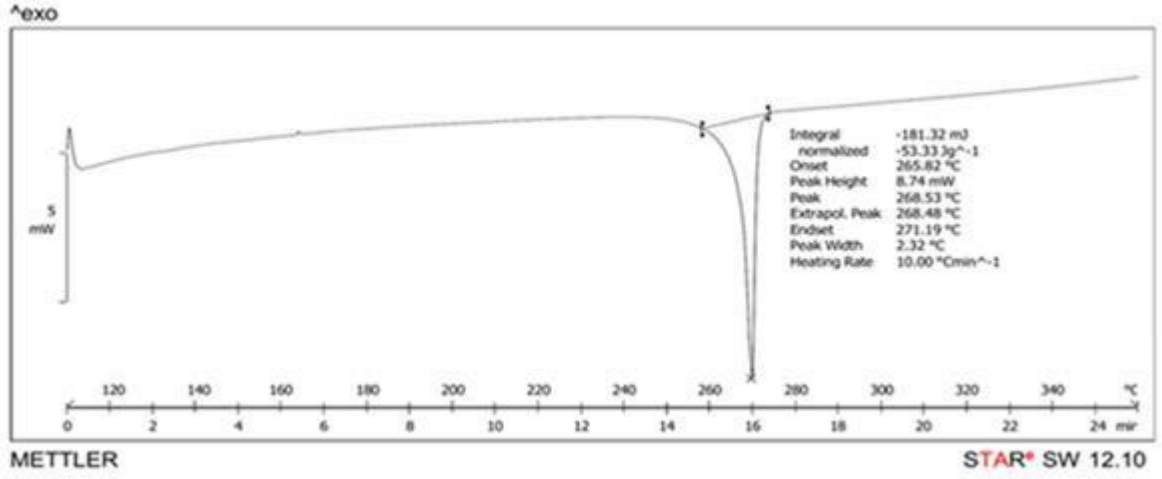

Figure 05: DSC graph of pure Resveratrol

X-Ray Diffraction Studies

The X-ray diffraction (XRD) analysis of Resveratrol reveals sharp, well-defined peaks at specific 2θ angles, confirming its crystalline nature. These distinct peaks demonstrate that Resveratrol predominantly exists in a crystalline form, which is crucial for maintaining its purity, stability, and functional performance. The positions of the 2θ values correspond to particular crystallographic planes, while the intensity of the peaks reflects the degree of crystallinity, influencing key properties such as solubility and bioavailability. Overall, the XRD results confirm the crystalline structure of Resveratrol, an important attribute for its pharmaceutical efficacy.

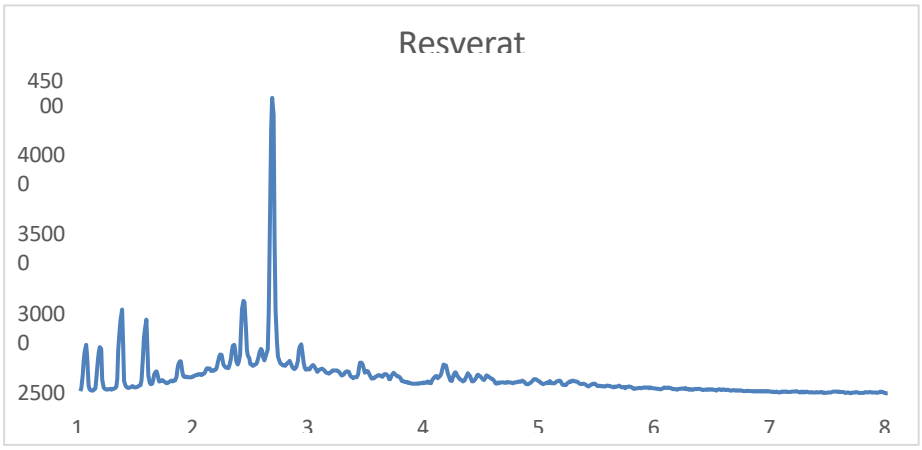

Figure 06: XRD graph of Resveratrol pure drug

Solubility in solid lipids

Table 07: Solubility of Solid lipid

Liquid lipid	Solubility of Resveratrol (mg/ml)
Glycerol monostearate	0.983
Stearic acid	1.47
Soya lecithin	0.869

Selection of the Liquid Lipid and Surfactant

The formulation of Nanostructured Lipid Carriers (NLCs) relies heavily on the careful selection of liquid lipids and surfactants to ensure optimal particle size, high drug-loading efficiency, and long-term stability. Liquid lipids are primarily chosen for their ability to effectively solubilize the active pharmaceutical ingredient (API), while surfactants are selected for their emulsification capacity and their role in maintaining the structural integrity of the NLCs.

Table 08: Solubility of Liquid lipid

Liquid lipid	Solubility of Resveratrol (mg/ml)
Castor oil	0.732
Triglyceride	1.436
Oleic acid	1.31

Table 09: Solubility of Surfactant

Surfactant	Solubility of Resveratrol (mg/ml)
Tween 20	0.524
Tween 40	0.638
Tween 60	0.057
Tween 80	1.59

Evaluation of Nanostructured lipid carriers.

Drug content

Table 10: Drug content (%) for Resveratrol

Formulation code	Drug Content (%)
RF1	93.87±1.25
RF2	89.17±0.69
RF3	91.74±0.45
RF4	95.21±0.98
RF 5	88.35±0.54

In Vitro release Study

Table 11: Drug release of RF1-RF5

Time(hr.)	RF1	RF2	RF3	RF4	RF5
0	0	0	0	0	0
1	25.86±1.02	21.56±1.65	25.65±1.29	29.47±1.11	20.94±1.58
3	44.23±0.14	39.60±1.51	42.58±1.05	49.89±1.54	38.48±1.02
4	58.76±0.87	54.59±0.65	57.31±1.52	60.54±1.65	53.63±1.55

5	67.39±1.02	60.36±1.36	66.63±0.98	69.78±1.47	59.42±1.34
6	72.84±0.66	67.82±1.46	70.98±0.62	75.34±0.92	66.38±1.09
7	84.54±0.81	79.92±0.76	82.84±0.0.91	88.69±0.73	78.64±0.29
8	92.32±1.05	87.63±0.85	91.36±0.44	94.77±1.26	86.48±0.36

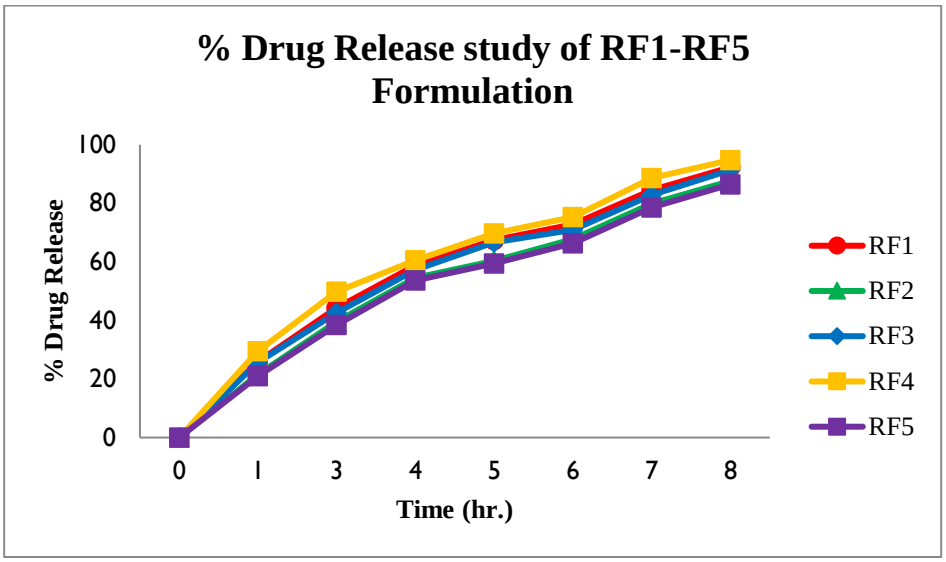

Figure 07: Drug release of RF1-RF5

Entrapment efficiency

Entrapment efficiency (%)

$$= \frac{\text{Total amount of drug added (mg)} - \text{Unentrapped drug (mg)}}{\text{Total amount of drug added (mg)}} \times 100$$

Table 12: Entrapment efficiency (%) of Resveratrol (RF4)

Formulation code	Entrapment efficiency (%)
RF4	95.38±0.15

Particle size analysis and Zeta potential

The particle size analysis of the Resveratrol (RF1-RF5) formulation reveals notable differences in their characteristics.

Table 13: Particle size analysis of (RF4) optimized Resveratrol loaded NLC formulation

Optimized Batch	Particle size (nm)	Zeta potential (mV)
RF4	196.2	-35.2

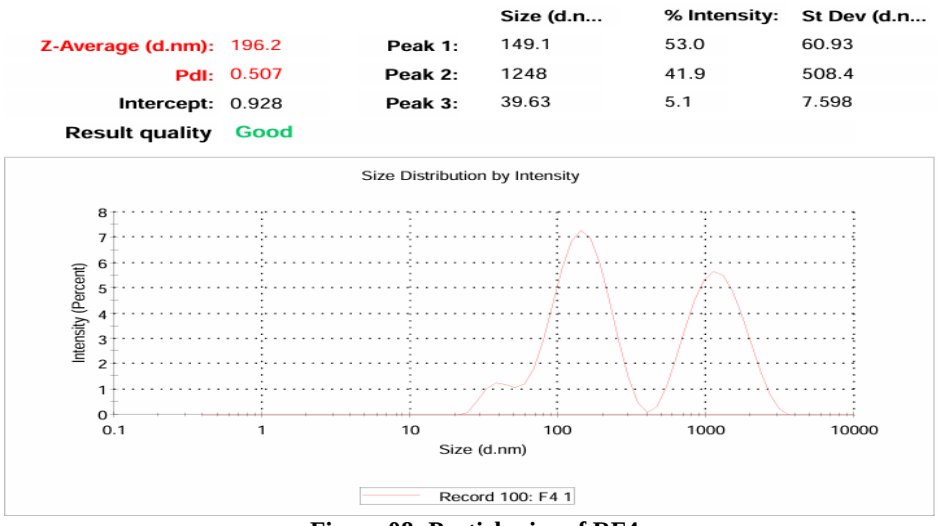

Figure 08: Particle size of RF4

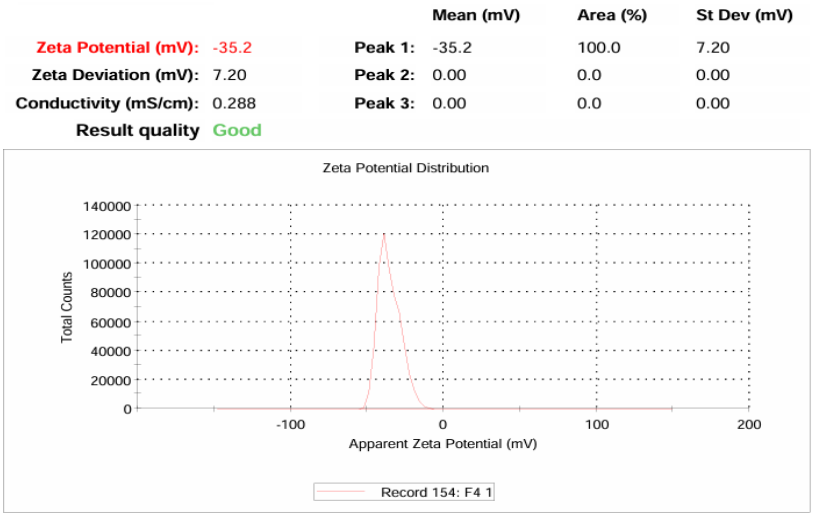

Figure 09: Zeta Potential of RF4

Characterization of NLCs

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) was carried out to determine the melting point of the drug and to assess the influence of excipients on its thermal behavior. The results revealed that no significant interaction occurred between the drug and the excipients.

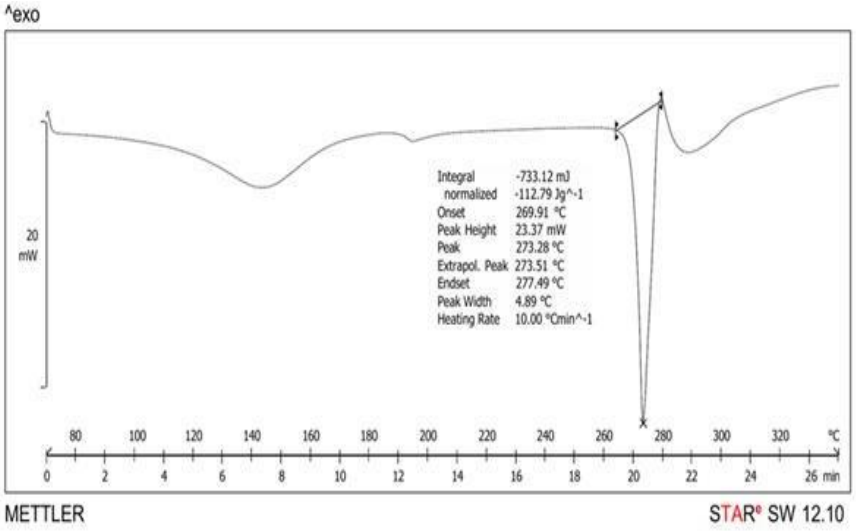

Figure 10: DSC graph of physical mixture of RF4

Stability Study

The stability studies of the optimized resveratrol NLC formulation indicated that there were no significant changes in its physicochemical properties. The observations from the stability studies showed that the formulation remained stable, with no noticeable variations in its physicochemical characteristics. Overall, the optimized resveratrol NLC formulation was found to be stable under accelerated stability conditions.

Table 14: Stability study results of Resveratrol optimized NLC formulation at accelerated stability condition

Formulation	Parameters	Accelerated Stability Study				
		0 Month	1 Month	2 Month	3 Month	6 Month
RF4	Particle size nm	195.12±1.02	195.12±1.45	195.12±1.11	195.11±1.32	195.07±1.05
	Zeta Potential (mV)	-34.1±0.85	-34.1±0.44	-34.1±1.02	-33.98±0.65	-33.96±0.47
	Drug release (%)	94.77±1.26	94.77±1.19	94.77±1.23	94.76±0.89	94.68±1.76

CONCLUSION

This research focused on the formulation of nanostructured lipid carriers (NLCs) containing resveratrol using the high-speed homogenization method. Preformulation studies were carried out to evaluate parameters such as appearance, melting point, and solubility. Design Expert software was employed to identify and optimize the critical factors influencing the formulation process.

Various analytical techniques were utilized to characterize the prepared NLCs. UV–visible spectroscopy and Fourier Transform Infrared Spectroscopy (FTIR) were used for chemical identification and to assess drug–excipient compatibility. DSC was conducted to investigate the thermal behavior of the drug and excipients & the melting process occurred maximum at 268.53 oC, while XRD analysis was performed to evaluate the physical state of resveratrol in its pure form and within the lipid matrix was found. This confirms crystalline structure.

A Box–Behnken experimental design was applied, considering both independent and dependent variables such as drug content, in vitro drug release, entrapment efficiency, particle size, and zeta potential. The optimized formulation (batch RF4) demonstrated a particle size of 196.2 nm, drug content 95.21 %, entrapment efficiency of 95.38%, and a cumulative drug release of 94.77 %. Stability studies conducted on the optimized batch (RF4) indicated no significant variations in physicochemical properties, confirming the formulation's stability and robustness.

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