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Design, Development and Evaluation f Nanostructured Lipid Carries Containing Resveratrol

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ABSTRACT

Aim*: To develop and evaluate Resveratrol-loaded Nanostructured Lipid Carriers (NLCs) for improved delivery, sustained release, and enhanced therapeutic potential in the management of diabetes mellitus.*

Objective*:The objective of this research is to overcome the limitations of conventional antidiabetic therapies by formulating optimized nanostructured lipid carriers (NLCs) and evaluating their physicochemical properties, drug loading, release profile, and particle morphology via TEM.*

Method*:Resveratrol-loaded NLCs were prepared using the high-speed homogenization method. Different formulations were developed by varying the concentration of solid lipids, liquid lipids, and surfactants. The prepared NLCs were characterized for particle size, zeta potential, drug loading capacity, and entrapment efficiency. TEM was used for morphological examination, and in vitro drug release studies were performed to determine release kinetics.*

Result*:FTIR analysis was performed to identify functional groups and assess drug–excipient compatibility, revealing no incompatibility between the components. DSC analysis was used to determine the melting point of the drug and evaluate the influence of excipients, confirming the absence of interactions. The in vitro drug release study demonstrated improved release characteristics. The optimized formulation (CF3) showed a particle size of 196.2 nm, high drug content (97.26%), and excellent entrapment efficiency (94.29%). TEM imaging revealed smooth, spherical particles, confirming successful NLC formation. Stability studies under accelerated conditions indicated good physical stability, with no significant changes in physicochemical properties. Overall, the results suggest that Resveratrol-loaded NLCs have strong potential as an effective drug delivery system.*

Key words:- *Solid lipid, liquid lipid, surfactant, resveratrol antidiabetic etc.*

INTRODUCTION

Resveratrol, a natural polyphenol, has shown promising antidiabetic and insulin-sensitizing effects in preclinical studies and even modest benefits in clinical trials (e.g., improved glycemic control and insulin sensitivity in type 2 diabetic patients). However, resveratrol's therapeutic potential is severely limited by its extremely low oral bioavailability (considerably <1%) due to extensive first-pass metabolism in the intestine and liver. These issues with resveratrol underscore the need for advanced drug delivery strategies to enhance their solubility, stability, and bioavailability for effective oral therapy. Nanotechnology-based delivery systems have emerged as promising solutions to such pharmaceutical challenges. In particular, Nanostructured Lipid Carriers (NLCs) are gaining attention for oral drug delivery of poorly soluble drugs. NLCs are biocompatible nanocarriers composed of a mixture of solid lipid and liquid lipid, stabilized by surfactants, forming a sub-micron colloidal matrix. NLC offered various advantages like enhanced solubility& stability, improved bioavailability, controlled release, combination etc.

MATERIALS AND METHODS

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 identified by different organoleptic characteristics.

Melting point

The melting point of Resveratrol was determined by introducing a tiny amount of drug into a small capillary tube, attaching this to the stem of a thermometer centred in a heating bath, heating the bath slowly, and observing the temperatures at which melting begins and is complete.

Solubility study of Resveratrol

Solubility study conducted by using shakes flask method. The solubility of Resveratrol was performed in Methanol, distilled water,phosphate buffer pH 7.4, Phosphate buffer pH 6.8, Acidic buffer pH 1.2.

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

a. Determination of Absorption Maxima i.e. λmax

The sample of the standard solution was scanned between 200-400 nm regions on UVspectrophotometer (Schimadzu 1800). The stock solution of the Resveratrol was prepared by dissolving 25 mg of drug in 25 ml of methanol, (1000 µg/ml) respectively. Then 0.1ml of above solution was diluted to 10 ml methanol to make 10 µg/ml solution.

b. Standard calibration curve of resveratrol by UV Spectroscopy.

- **Calibration Curve of Resveratrol in Methanol**

Preparation of stock solution in Methanol:

Standard stock solution was prepared by taking 50 mg in 50 ml of Methanol (1000µg/ml). The stock solution scanned in the range 400-200 nm by UV spectrophotometer the solution showed maximum absorbance at 304 nm.

Preparation of dilutions for the standard curve:

From 1000µg/ml, prepare solutions of 2, 4, 6,8,10 and 12 ppm by diluting100 -500 µl stock to 10 ml Methanol. Absorbance was taken at 304 nm using Methanol as a blank. The absorbance v/s concentration graph is plotted.

FTIR Spectroscopy[10,11]

FT-IR is used both together information about the structure of a compound and as an analytical tool to assess the purity of a compound. The infrared spectrum sample was recorded and the spectral analysis was done. The dry sample of drug was taken & directly placed and analyzed by FTIR (Perkin Elmer) instrument. IR spectroscopy is one of the important analytical techniques for chemical identification. The drug and excipient interaction were studied by FTIR spectroscopy. The spectra were recorded for pure drug using FTIR. The scanning range was 400-4000 cm-1.

DSC Thermogram[12]

DSC thermogran highlights the differences in the thermal behaviour of resveratrol which can be useful in identifying & characterizing compounds. Thermal analysis was conducted for the pure Resveratrol powder, their physical mixtures of NLC. Five milligrams of each sample was accurately weighed and placed into aluminium crucible and sealed using an aluminium lid by a sealing machine. The thermograms were obtained by differential scanning calorimetry at a heating rate of 10°C/min. This was done in an inert atmosphere flushed with nitrogen at a rate of 30 ml/min, and Al_2O_3 was used as a reference.

XRD studies of pure drug[13]

This study is carried out to study the physical properties of the Resveratrol in pure form and inside the lipid matrix.

The X-ray diffraction (XRD) patterns of NLCs were determined using XRD diffractometry (D8 ADVANCE, Bruker AXS Inc, Madison, WI). Study was performed on a Siemens DIFFRAC plus 5000 powder diffractometer with Cu / 40 kV/ 30 mA. The tube voltage and amperage were set at 40 kV and

30 mA, respectively. Each sample was scanned between 10◦C and 90◦C in 2θ with a step size of 0.01◦C at 1 step/ scanning speed of 10.0000 deg/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.

1. Briefly, weighed Stearic acid and Triglyceride and the resveratrol were dissolved into 10 ml of mixed organic solvent of Methanol in a water bath at 55 °C.
2. The mixture was then added drop wise to Tween 80 at 70^0C a pre-emulsion was obtained by homogenization at 15000 rpm and ultrasonicate for 30 min at 70^0C.
3. Further, this pre-emulsion was ultra sonicated for 15 min to prevent the crystallization of lipids.
4. The o/w emulsion obtained was subsequently cooled down to room temperature with continuous stirring and the lipid was recrystallized to form Nanostructured lipid carrier (NLC).

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
			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	1500
RF2	100	3.5	0.735	0.315	1.5	1500
RF3	100	2	0.42	0.18	1	1500
RF 4	100	2	0.42	0.18	1.25	1500
RF 5	100	3.5	0.735	0.315	1.25	1500
RF 6	100	5	1.05	0.45	1.25	1500
RF 7	100	2	0.42	0.18	1.5	1500
RF 8	100	5	1.05	0.45	1.5	1500
RF 9	100	3.5	0.735	0.315	1	1500

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 methanol. The percentage of resveratrol in each formulation was quantified spectrophotometrically by measuring the absorbance of the clear supernatant at a maximum wavelength of 304 nm. Each experiment was conducted in triplicate, using acetonitrile as the blank for UV absorbance measurements.

In Vitro release Study

The in vitro release of resveratrol from NLCs was evaluated using the dialysis bag method. The study was performed at 37 °C using phosphate buffer (pH 6.8) as the release medium. A 2 mL aliquot of the resveratrol-loaded NLC formulation was accurately measured and transferred into the dialysis membrane. The formulation was gently positioned to ensure proper contact with the membrane surface. The dialysis bag was immersed in 100 mL of phosphate buffer (pH 6.8) in the reservoir compartment, which served as the receiving medium. The setup was maintained on a magnetic stirrer at 75 rpm and 37 °C. At predetermined intervals (1, 2, 3, 4, 5, and 6 h), 5 mL samples were withdrawn from the receiving compartment and analyzed spectrophotometrically at 304 nm to determine the amount of drug released. After each sampling, an equal volume of fresh phosphate buffer was added to maintain sink conditions. All experiments were conducted 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:

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

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 (RF2) 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 thermograms 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

Active Pharmaceutical Ingredient: Resveratrol

Melting point

The melting point of Resveratrol was determined using capillary tube method. Sample filled in capillary is tied with thread to the thermometer and suspended into Thieles tube and heated till drug powder melts.

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

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 Methanol, DMSO, and PEG

Sr.no.	Drug	Solvent	Solubility status
1	Resveratrol	Methanol	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

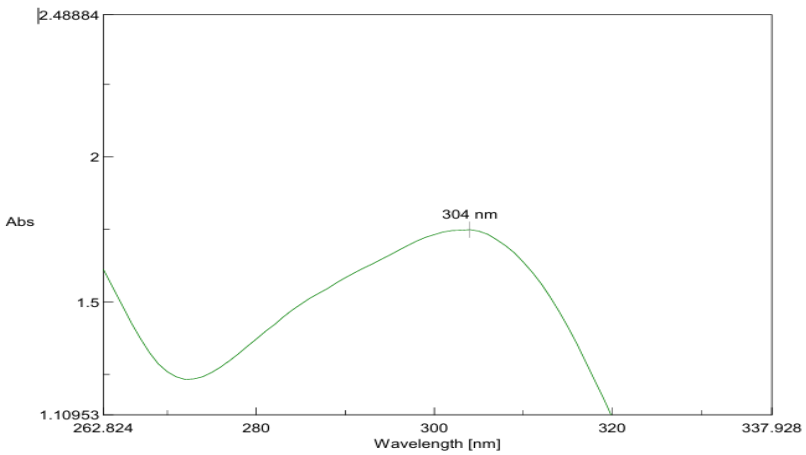

Figure 01: UV spectrum of Resveratrol in methanol (10µg/ml)

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 Methanol**

Table 06: Calibration Curve of Resveratrol in Methanol

Concentration (µg/ml)	Absorbances
0	0
2	0.0547
4	0.1012
6	0.1541
8	0.2101
10	0.2514
12	0.3018

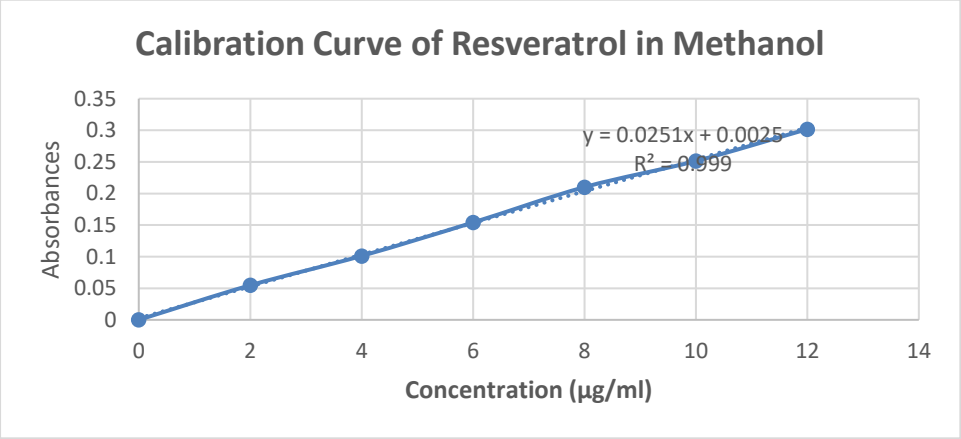

Figure 02: Calibration Curve of Resveratrol in Methanol

FTIR Spectroscopy

- **FTIR of Resveratrol**

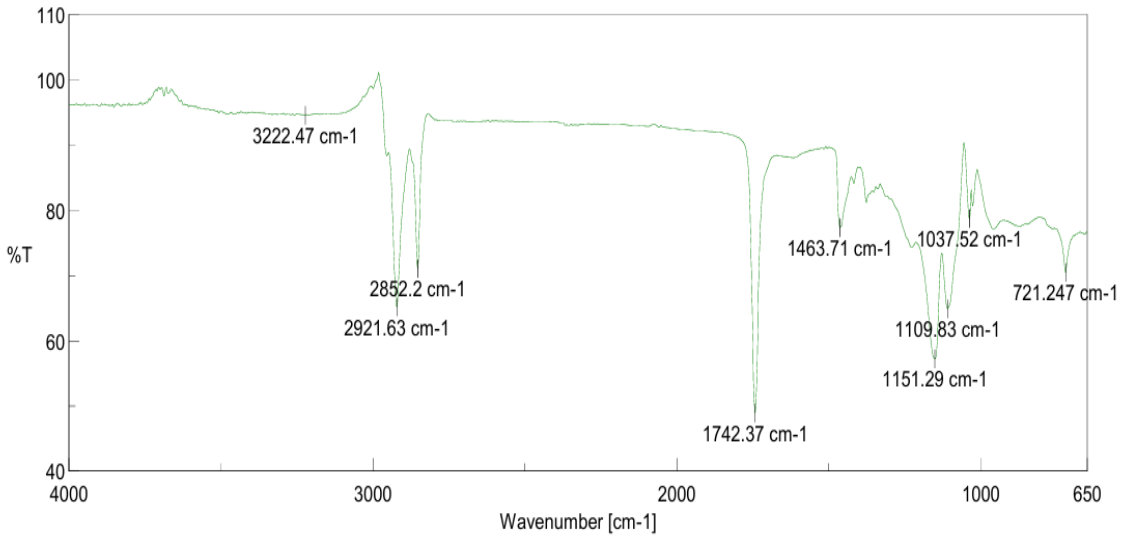

Figure 03: IR spectra of Resveratrol

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**

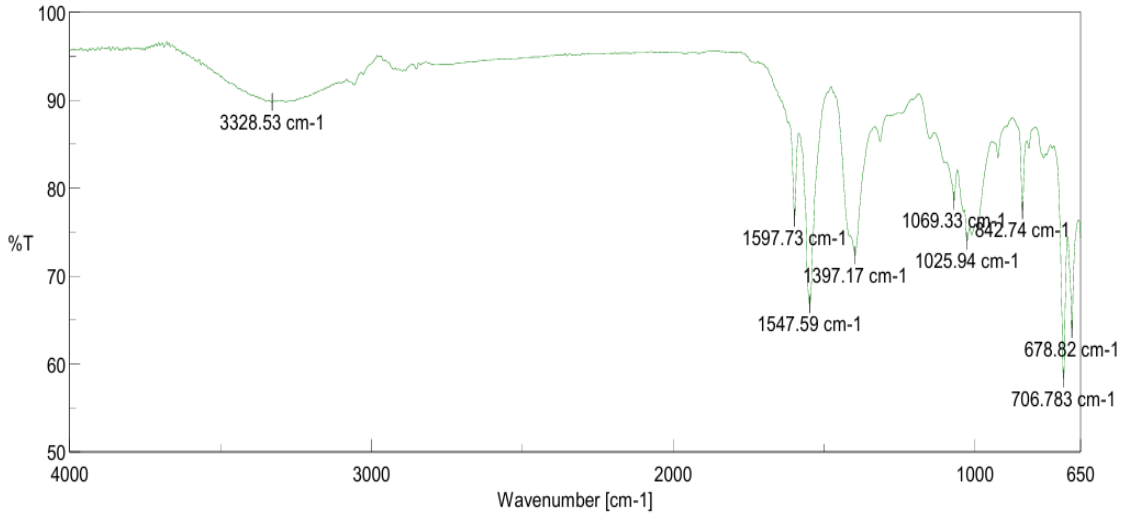

Figure 04: IR spectra of Resveratrol Physical mixture

Analyzing the FTIR spectra of a 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 shows that there is no any incompatibility of Resveratrol with the excipients.

The groups showing for the physical mixture corresponding to the vibration frequencies of pure Resveratrol drug.

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

m

DSC Thermogram

DSC Thermogram Analysis

The DSC thermograms of Resveratrol are depicted in below. For pure and physical mixture of Resveratrol the melting process occurred with a maximum peak at 268.53°C.

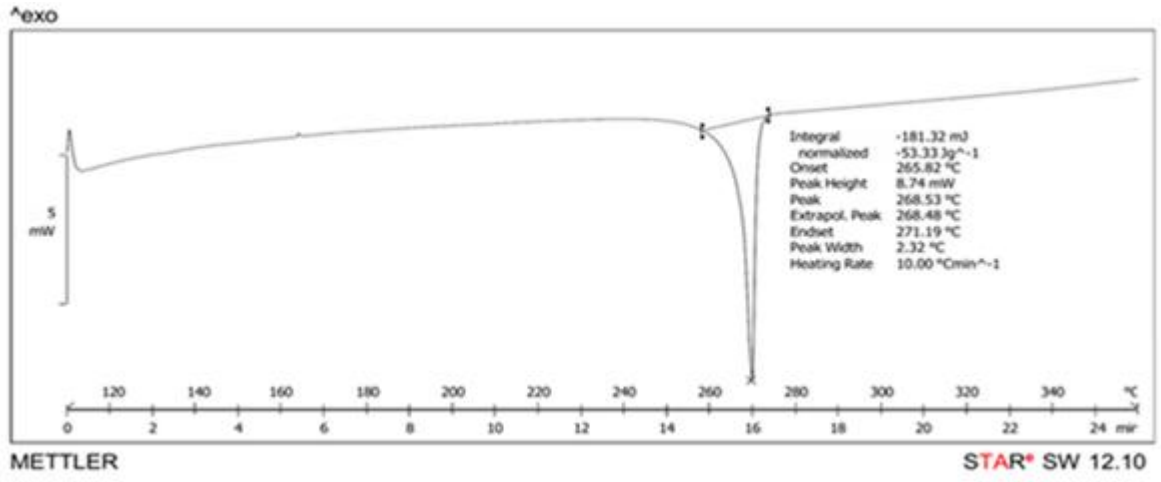

Figure 05: DSC graph of pure Resveratrol

X-Ray Diffraction Studies

The X-ray diffraction (XRD) pattern of Resveratrol displays clear peaks at defined 2θ angles, confirming its crystalline structure. These sharp, well-defined peaks indicate that Resveratrol is primarily in a crystalline state, which is essential for evaluating its purity, stability, and performance.

The 2θ values obtained correspond to the crystallographic planes, and its peak intensity indicates the degree of crystallinity, which affects drug solubility and bioavailability. The XRD analysis confirms that Resveratrol is crystalline, which is important for its pharmaceutical properties.

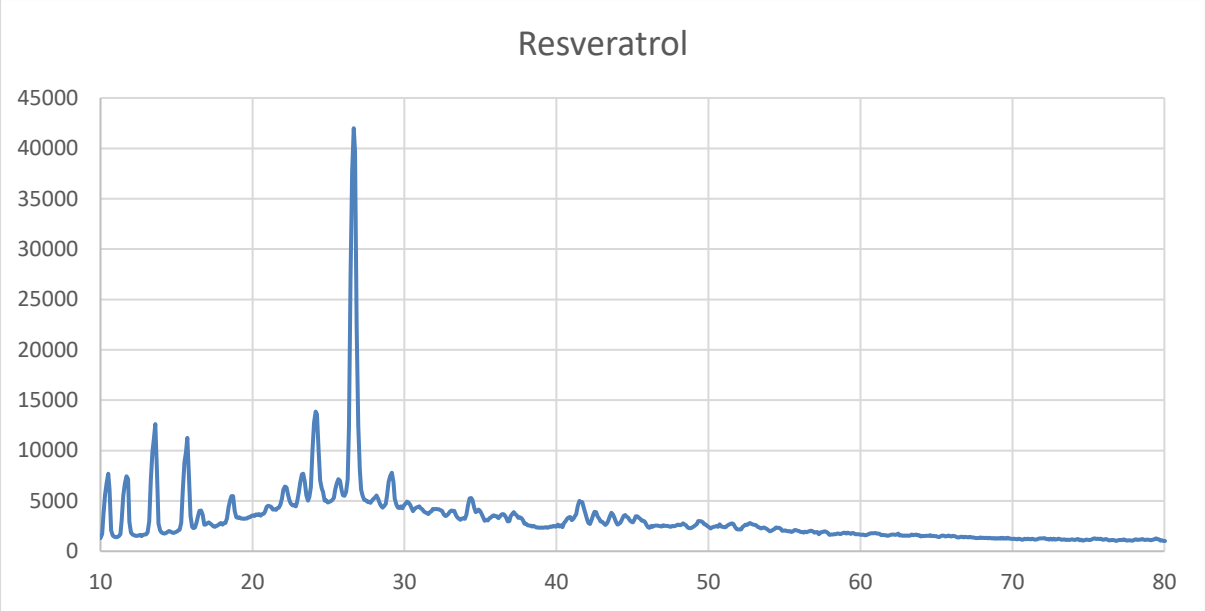

Figure 06: XRD graph of Resveratrol pure drug

Solubility in solid lipids

Table 07: Solubility of Solid lipid

Liquid lipid	Solubility of Resveratrol (mg/ml)
Glycerol monostearate	0.985
Stearic acid	1.56
Soya lecithin	0.875

Selection of the Liquid Lipid and Surfactant

The selection of liquid lipids and surfactants for Nanostructured Lipid Carriers (NLCs) is crucial for achieving desired particle size, drug loading capacity, and stability. Liquid lipids are chosen based on their

ability to solubilize the active pharmaceutical ingredient (API), while surfactants are selected for their emulsification efficiency and ability to stabilize the NLC.

Table 08: Solubility of Liquid lipid

Liquid lipid	Solubility of Resveratrol (mg/ml)
Castor oil	0.723
Triglyceride	1.468
Oleic acid	1.27

Table 09: Solubility of Surfactant

Surfactant	Solubility of Resveratrol (mg/ml)
Tween 20	0.522
Tween 40	0.622
Tween 60	0.042
Tween 80	1.63

Evaluation of Nanostructured lipid carriers.

Drug content

Table 10: Drug content (%) for Resveratrol

Formulation code	Drug Content (%)
RF1	93.45±1.25
RF2	97.26±0.98
RF3	89.45±1.45
RF 4	90.17±1.36
RF 5	88.72±1.04
RF 6	94.23±0.87
RF 7	89.12±1.54
RF 8	96.37±1.74
RF 9	89.7±1.58

In Vitro release Study

Table 11: Drug release of RF1-RF9

Time (hr.)	RF1	RF2	RF3	RF4	RF5	RF6	RF7	RF8	RF9
0	0	0	0	0	0	0	0	0	0
1	20.86±1.02	38.47±1.11	23.85±0.65	33.56±1.65	22.49±1.32	39.37±1.11	21.94±1.58	32.65±1.36	22.68±1.36
2	45.36±0.25	58.15±1.06	36.98±1.47	41.25±1.04	34.53±0.87	46.32±1.05	33.65±1.36	43.21±1.41	33.54±1.01
3	64.23±0.14	63.89±1.54	48.24±1.58	54.63±1.51	49.32±1.65	68.76±1.23	43.48±1.02	60.58±1.05	49.67±0.52
4	75.56±0.87	76.54±1.65	64.38±1.65	62.59±0.65	63.89±1.41	74.31±1.04	59.63±1.55	71.31±1.52	57.61±1.62

5	81.56±1.02	84.78±1.47	71.56±1.47	75.36±1.36	72.63±1.32	83.54±0.65	73.42±1.02	84.63±0.98	71.34±0.87
6	92.32±1.05	95.3±1.02	80.14±1.32	85.63±0.85	87.45±0.87	92.48±0.74	82.48±0.36	92.36±0.44	83.6±0.69

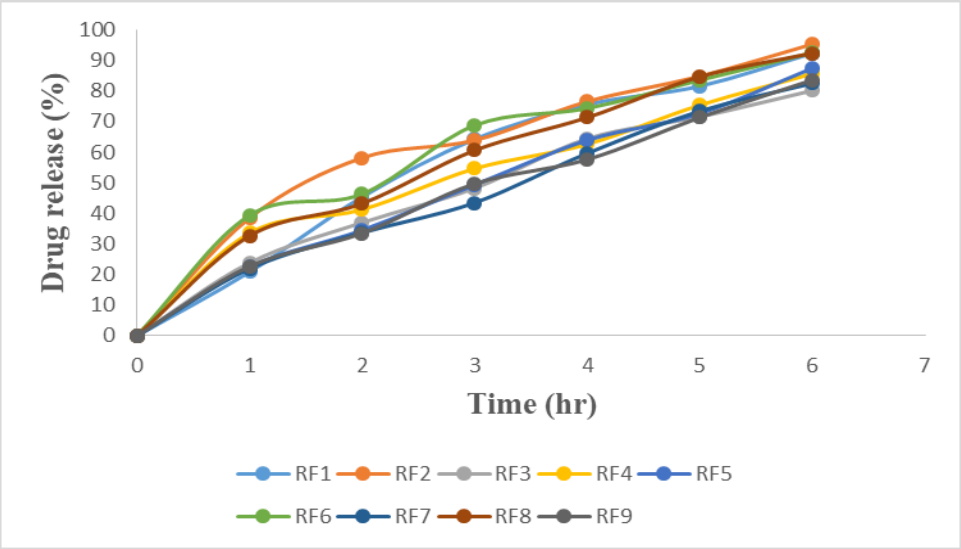

Figure 07: Drug release of RF1-RF9

Entrapment efficiency

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

Table 12: Entrapment efficiency (%) of Resveratrol (RF2)

Formulation code	Entrapment efficiency (%)
RF2	94.29±0.15

Entrapment efficiency % = 94.29

Particle size analysis and Zeta potential

The particle size analysis of the Resveratrol (RF1-RF9) formulation reveals notable differences in their characteristics.

Table 13: Particle size analysis of Resveratrol (RF1-RF9) NLC formulation

Optimized Batch	Particle size (nm)	Zeta potential (mV)
RF2	196.2	-35.2

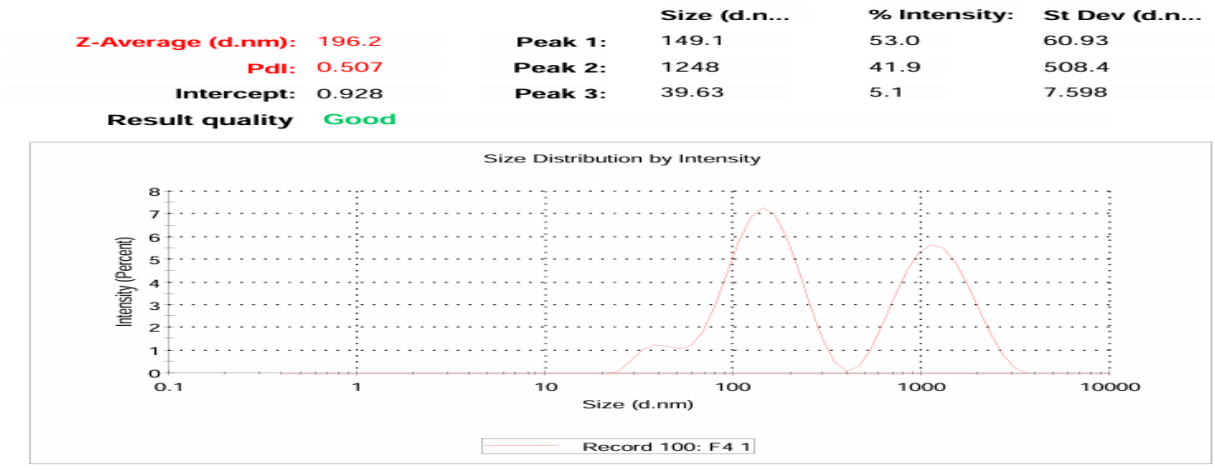

Figure 08: Particle size of RF2

			Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV):	-35.2	Peak 1:	-35.2	100.0	7.20
Zeta Deviation (mV):	7.20	Peak 2:	0.00	0.0	0.00
Conductivity (mS/cm):	0.288	Peak 3:	0.00	0.0	0.00
Result quality	Good				

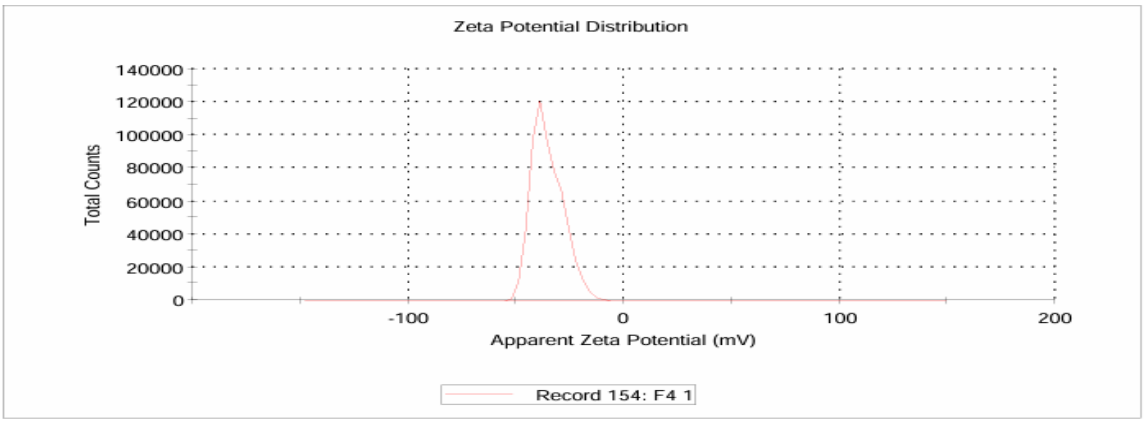

Figure 09: Zeta Potential of RF2

Characterization of NLCs

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) was performed to determine the melting point of the drug and to evaluate the effect of excipients on it. The results indicated no interaction between the drug and the excipients.

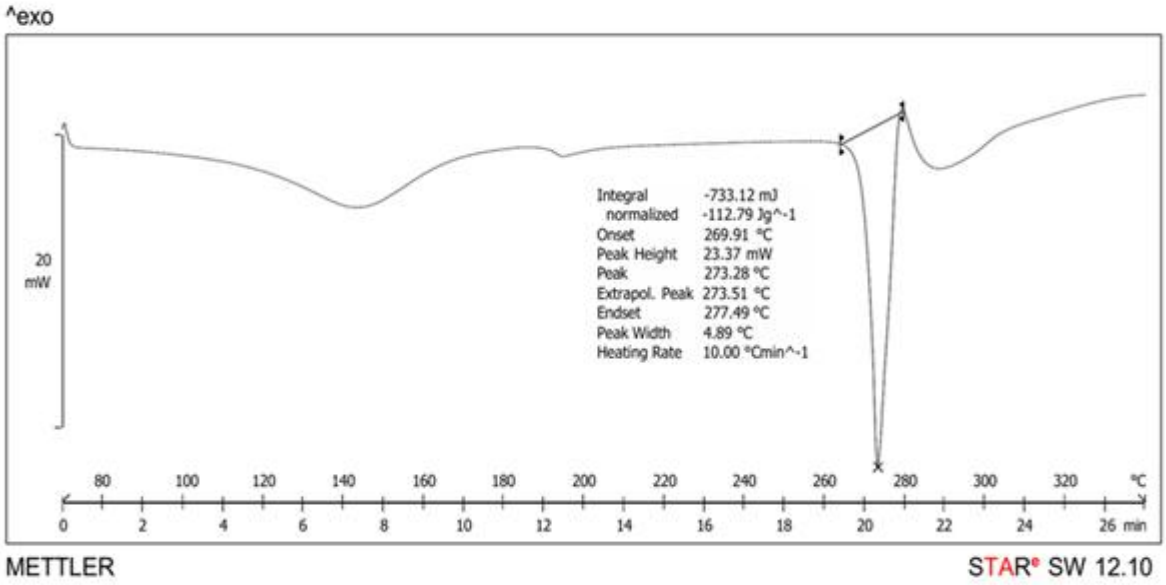

Figure 10: DSC graph of physical mixture of RF2

Stability Study

The stability studies of Resveratrol optimized NLC formulation indicate that there were no significant changes in the physico-chemical properties of the formulation. Following are the observations of stability studies. There were no significant changes in physico-chemical characteristics.

It was observed that the optimized Resveratrol NLC formulation is stable at accelerated stability conditions.

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

Drug	Parameters	Accelerated Stability Study				
		0 Month	1 Month	2 Month	3 Month	6 Month

Resveratrol	**Particle size nm**	195.12±1.02	194.55±1.45	194.20±1.11	193.15±1.32	191.04±1.05
	Zeta Potential (mV)	-34.1±0.85	-34.1±0.44	-33.55±1.02	-33.45±0.65	-33.05±0.47

CONCLUSION

This research involved formulation of NLC containing resveratrol using high speed homogenizer method. Preformualtion study conducted like appearance, melting point, solubility Design expert software is used for determining the factors influencing formulation. Various studies carried out for evaluation of NLCS like UV spectroscopy, FTIR for chemical identification as well as drug and excipient compatibility study, DSC for identifying & characterizing thermal behaviour of drug and excipients, XRD for physical properties of the Resveratrol in pure form and inside the lipid matrix. Independent and Dependent variables in Box–Behnken design, drug content, invitro drug release, entrapment efficiency, particle size & zeta potential. Particle size of RF2 was found 196.2 nm, entrapment efficiency 94.29%, and drug release 95.3±1.02. Optimized formulation batch i.e. RF2 was placed for stability study and found that there were no significant changes in the physico-chemical properties of the formulation

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