RESEARCH ARTICLE

Formulation and Characterizationof Nanostructured Lipid Carrier (NLC) Based Gel for Topical Delivery of Resveratrol

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ABSTRACT
Nanostructured lipid carriers based topical gel of Resveratrol was created with the aim of reducing inflammation. NLC is made up of propylene glycol as the co-surfactant, tween 20 as a surfactant, oleic acid as a liquid lipid, & stearic acid as a solid lipid. Particle size, SEM, DSC & FTIR were primarily utilised for analysing NLCs produced via solvent emulsification process. High entrapment efficiency, comprising 56.47% to 85.10%, has been demonstrated by the whole NLC. With 62.80nm of typical particle size & a 0.323 polydispersity index, which indicates uniformity in the distribution of particle sizes, formulation F1 was determined as the best formulation. Formulation F1's stability is shown by its larger zeta potential magnitude. The nanoparticulate dispersion was appropriately gelled & evaluated for in-vitro permeation study, homogeneity, spreadability, and physical appearance. The developed NLCs dispersion gel's in-vitro drug release pattern demonstrated both burst & prolong release. It was determined that resveratrol's created NLC gel shows promise for the drug's extended availability in skin tissues and may be applied to improve the treatment of inflammatory diseases.
Keywords: Resveratrol, Nanostructured Lipid Carrier (NLC), Topical Gel, Nanoparticle
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INTRODUCTION
The creation of nanodevices that distribute medications in a regulated and continuous manner is a component of nanostructures. These nanodevices contain polymeric nanoparticles (chitosan nanoparticles, PLGA nanoparticles) and colloidal carriers like lipids (solid-lipid nano-particles (SLN) & NLCs, etc.) [1,2]. With a plethora of properties for transdermal applications, NLCs or new generation technologies for colloidal lipid carriers, show promise in transdermal medication administration. Since their discovery in the 1900s, solid lipid nanoparticles (SLNs) have outperformed alternative colloidal systems in terms of physical stability, drug half-life, and high biocompatibility (Muller, Maassen, Weyhers, and Mehnert 1996). On the other hand, the low concentration of nanoparticles in the SLNs system (1% to 30%) and the phenomena of drug ejection are explained by the flawless lipid crystals of solid lipid limiting drug solubility [3].

The biocompatibility, drug targeting suitability, manufactured release capability, ease of fabrication, and large-scale production are among the key advantages of nanostructured lipid-based systems. It does, however, have several drawbacks, such as drug loading and medication stability in preservation. The liquid lipid in nano-structured lipid carriers (NLC) is meant to enhance system homogeneity and drug loading. Both liquid & solid lipids make up NLC [4]. Lipid particles' close contact with stratum corneum is ensured via its small size & may enhance volume of medication that absorbs through skin or mucosa. Such carriers offer a controlled release because of their solid-lipid matrix. This technique is essential when a medication needs to be administered over a longer period, when systemic absorption must be minimized, or when a substance causes irritation at higher doses [5].

Long-term medication therapy for inflammatory conditions like arthritis invariably calls for an oral delivery method with the fewest possible stomach side effects. The transdermal method enhances patient compliance by enabling control and prolong elimination of active component. Topical approach prevents first pass metabolism, boosts patient compliance, and eliminates adverse effects related to gastrointestinal tract. Consequently, goal of developing topical delivery vehicles is to alter the way that drugs penetrate the skin [6,7]. It has been demonstrated that NLCs can finely control release kinetics and shield poorly soluble antihypertensive medications and Vaso protective nutraceuticals from fast degradation by increasing their bioavailability. One such product is resveratrol (RES). When used in conjunction with conventional antihypertensive medication, resveratrol has been demonstrated to improve blood pressure decrease. Its anti-inflammatory and antioxidant qualities are responsible for this [8]. The modified NLC preparation effectively administered this medicine transdermally by improving bilayer fluidity through lipids and surfactants,

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Table 1: Composition of NLC

Ingredients	F1	F2	F3	F4
Resveratrol	0.2gm	0.2gm	0.2gm	0.2gm
Stearic Acid	0.8gm	0.8gm	0.8gm	0.8gm
Oleic Acid	0.2gm	0.2gm	0.2gm	0.2gm
Tween 20	0.5gm	-	-	-
Tween 40	-	0.5gm	-	-
Tween 60	-	-	0.5gm	-
Tween 80	-	-	-	0.5gm
Propylene Glycol	0.25gm	0.25gm	0.25gm	0.25gm
Water	Q.S to 50ml	Q.S to 50ml	Q.S to 50ml	Q.S to 50ml

Table 2: Composition of RES loaded NLC gel

Ingredients	F1	F2	F3	F4
Carbopol	1	1.5	1	1.5
Resveratrol	1	1	-	-
RES-NLC	-	-	1	1
Glycerine	2gm	2.5gm	3gm	2gm
Triethanolamine	Q.S	Q.S	Q.S	Q.S
Distilled Water	Q.S to 100ml	Q.S to 100ml	Q.S to 100ml	Q.S to 100ml

Table 3: Calibration curve of Resveratrol in different buffer solution

Conc (mcg/ml)	Abs. (0.1N HCl pH 1.2)	Abs. (pH 6.8 Buffer solution)	Abs. (pH 7.4 Buffer solution)
0	0	0	0
2	0.033	0.029	0.097
4	0.046	0.067	0.237
6	0.066	0.083	0.304
8	0.093	0.108	0.407
10	0.119	0.138	0.492

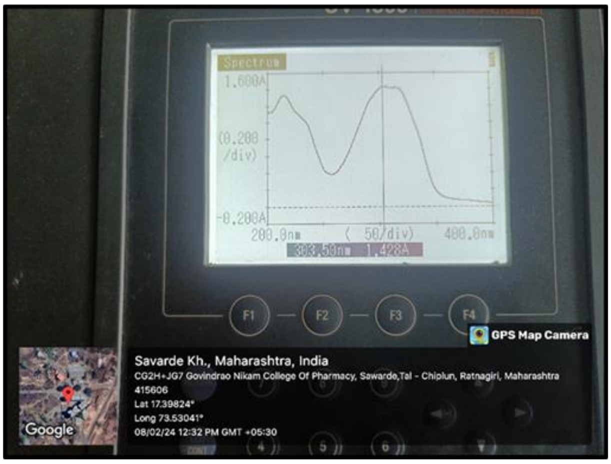

Figure 1: UV Spectra of Resveratrol

consequently raising topical bioavailability & sustaining therapeutic levels within the layers of skin [9].

MATERIALS AND METHODS

Materials

Vital Herbs, Delhi provides Resveratrol. Stearic acid, Oleic acid, Glycerol Monostearate, Tween 20, Tween 40, Tween 60, Tween 80, Sodium Dihydrogen Phosphate, Dialysis

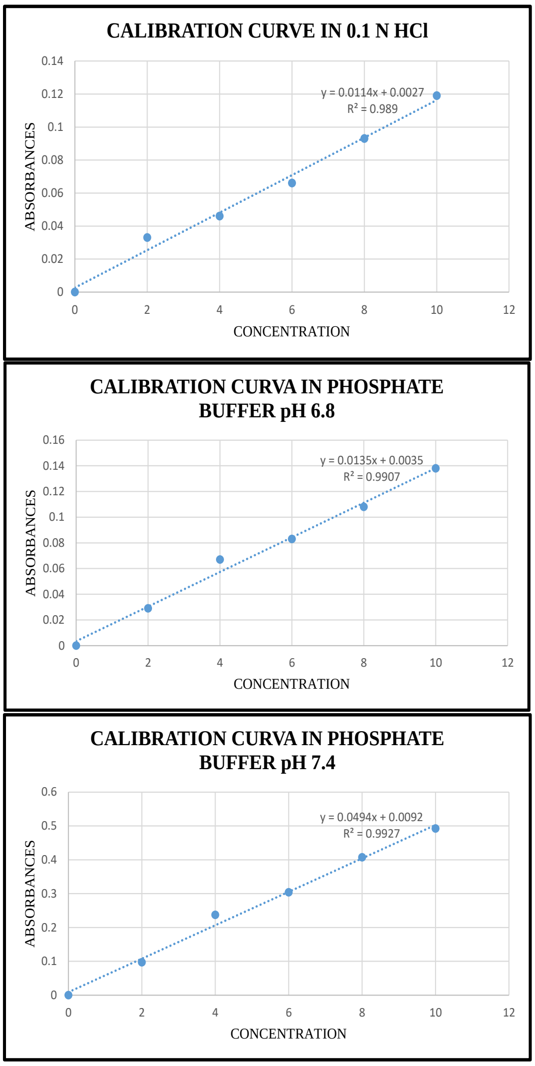

Figure 2: Calibration curve of Resveratrol in 0.1N HCl, Phosphate buffer (pH 6.8) & (pH 7.4)

Membrane 12 KDa Himedia, 2,2-dipenyl-1-picrulhydrazyl and Loba Chemicals is the source of other necessary chemicals. All of the studies were carried out using water that had been double-distilled.

Methods

Preparation of Resveratrol loaded NLC

RES-NLCs were prepared using a solvent emulsification method. Briefly, stearic acid (800 mg) and oleic acid (200 mg) were mixed together and then were heated at 75°c through constant stirring.

The preparation of a solution of aqueous involved dissolving Tween (20, 40, 60, 80) (500 mg) in water (Q.S. to 50ml) respectively followed by heating at 75°c. In this aq. To achieve the final mix (50 ml), the solution of surfactant was added or injected to the heated lipid phase using a needle (24 gauge) at a stirring rate of 600rpm. For 40mins at 75°C, the resulting mixture was swirled to improve the emulsification.[10] NLC's composition is listed in Table 1.

Preparation of Resveratrol loaded NLC Gel

As mentioned in previous characterizations (particle sizeNLC dispersion's in vitro release profile & entrapment efficiency) the best physicochemical features of an NLC formulation were chosen. The composition of RES loaded NLC gel are shown in Table 2. NLC gel is created by mixing an aqueous dispersion of Carbopol 940 in a modest amount of distilled water, that proceeded to hydrate for 4-5 hours. Glycerol (10%w/w) subsequently adds up into aqueous dispersion & NLC equivalent to 1% of Resveratrol was also added into it and Resveratrol pure drug (1%). Adding Triethanolamine into above dispersion by magnetic stirrer at speed of 800rpm. Stirring was kept up until the Carbopol got dispersed, then leave the gel overnight in order to remove any trapped air.[11]

Characterization of NLCs

Size of Particle & Zeta potential: A HORIBA SZ-100 was used to identify the optimized RES-NLCs' mean size of particle & zeta potential. RES-NLCs were appropriately neutralized with deionized water before being used for analysis [12].

Drug Entrapment Efficiency

After centrifuging the aqueous dispersion, the ratio of integrated resveratrol (entrapment efficiency) was calculated by spectro-photometric measurement at 303nm utilizing a Shimadzu UV-1800. Quantity of integrated drug is calculated by minus free drug from original drug & free drug quantity was determined in the supernatant [13]. This

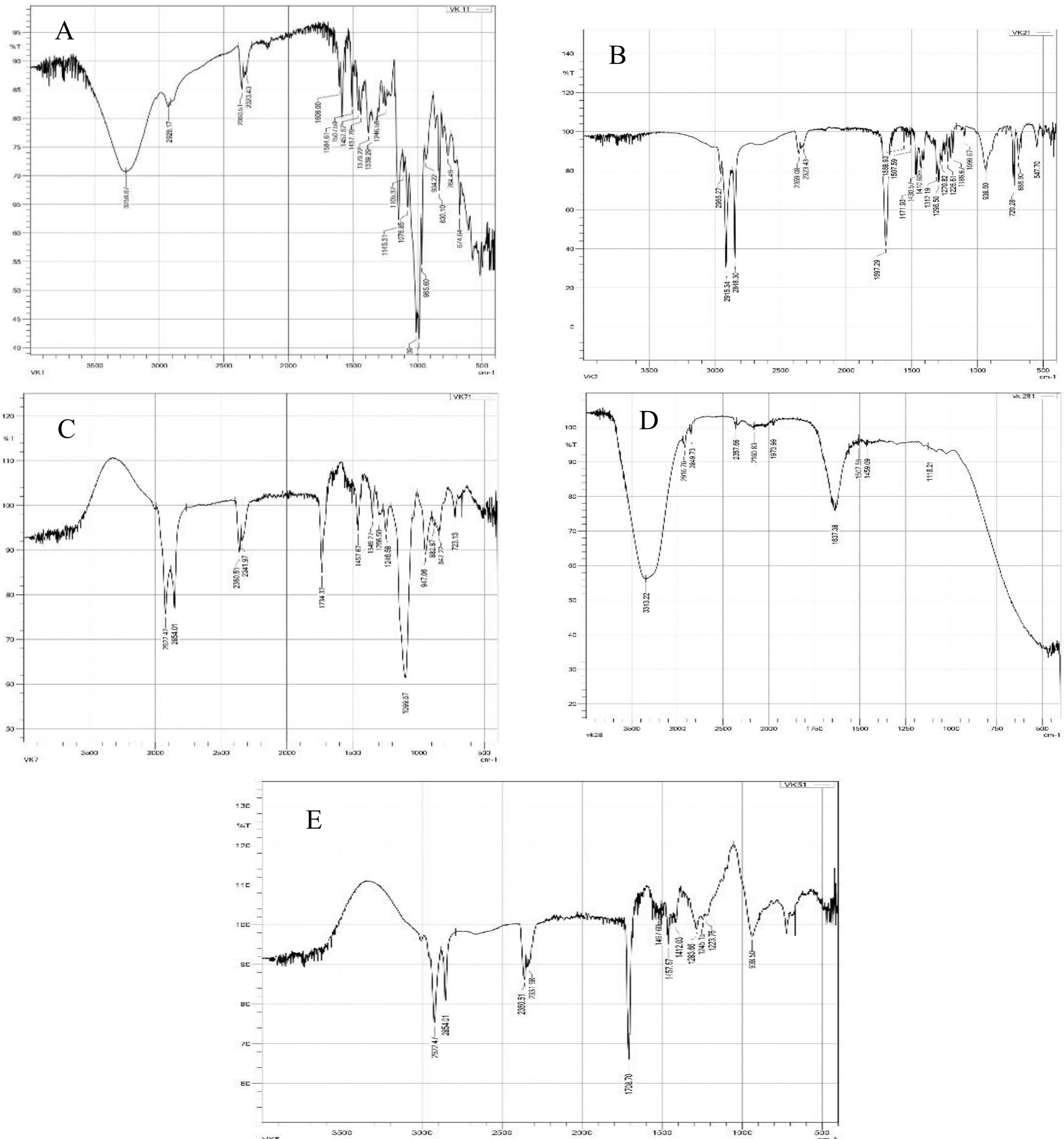

Figure 3: FTIR spectra of (A) Resveratrol Pure Drug, (B) NLCs physical mixture, (C) Physical Mixture of Gel, (D) Final Formulation of NLC and (E) Final Formulation of Gel

formula could be used to determine the entrapment efficiency:

$$EE\ (\%) = (W_{initial\ drug} - W_{free\ drug} / W_{initial\ drug}) \times 100$$

Fourier Transformed Infrared (FT-IR) Spectroscopic Analysis

The characteristic peaks of each functional group found in sample can be seen in an IR spectrum. FTIR analyses were performed on the drug, their physical combinations, and formulations to ensure effective entrapment. Using an IR Spectrophotometer (Shimadzu model 7600S), Pure resveratrol's infrared spectra, gel's physical mixture, NLC's physical mixture, NLC formulation, and gel formulation were all documented. The spectrophotometer's range was 500/cm to 4000/cm [14].

Differential Scanning Calorimetry (DSC)

Pure Resveratrol, physical mixture of NLC, physical mixture of Gel, Formulation of NLC and Formulation of Gel were subjected to DSC analyses. Precisely weighed specimens were meticulously positioned within DSC vessels, and heating patterns were documented throughout range of 25–350°C temperature at 10°C per min heat in inert environment (N2 8 mL per min). A differential scanning calorimeter (Hitachi DSC-7020) was chosen for this investigation [15].

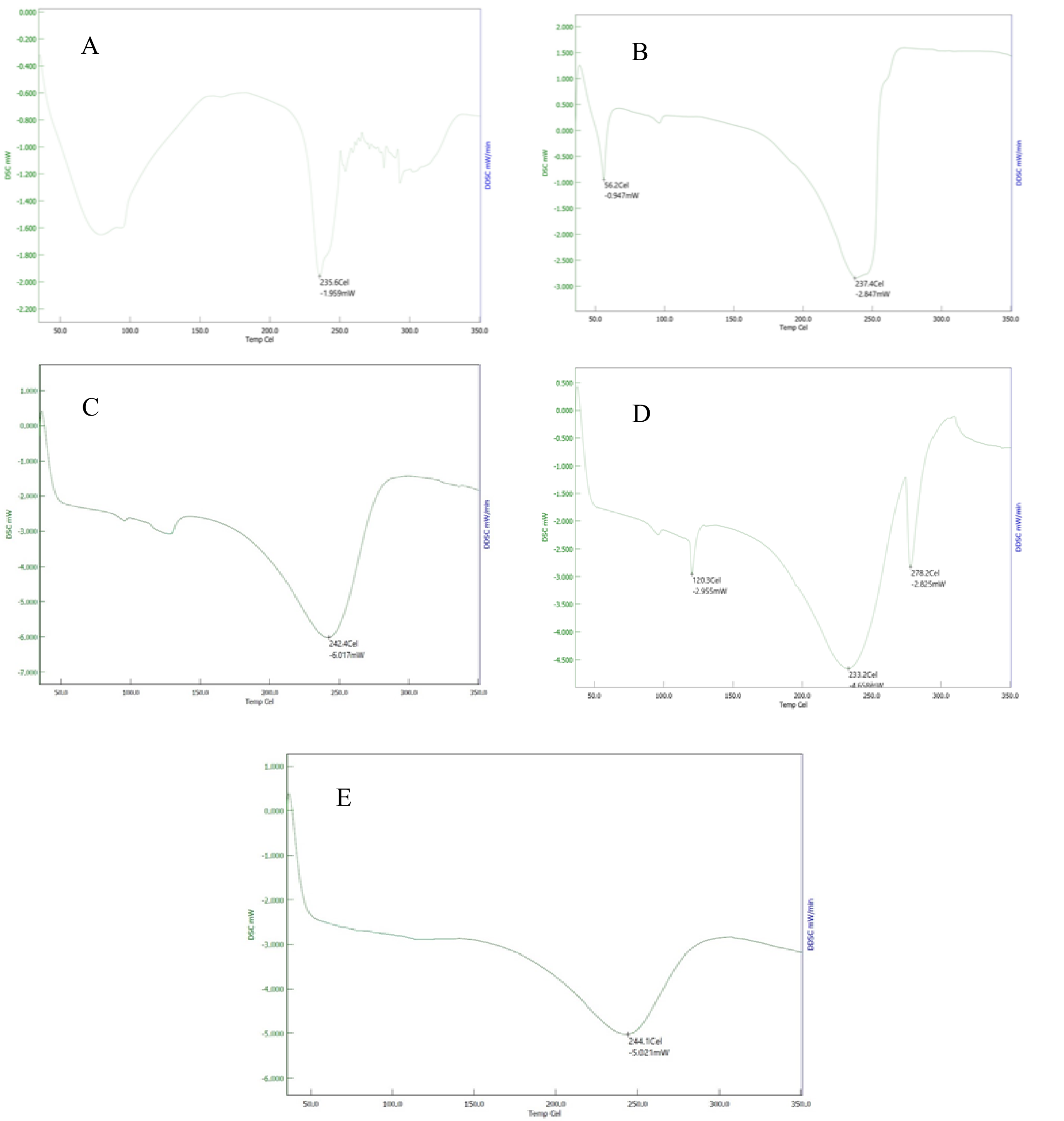

Figure 4: DSC of (A) Resveratrol Pure Drug (B) NLCs physical mixture (C) Physical Mixture of Gel (D) Final Formulation of NLC & (E) Final Formulation of Gel

Table 4: DPPH Assay

Concentration (µg/ml)	% Antioxidant Activity of Resveratrol	% Antioxidant Activity of Ascorbic Acid
10	11.76	21.83
20	24.57	31.83
40	35.29	43.16
60	53.45	58.82
80	77.24	74.49
100	88.76	92.15

Table 5: Size of Globule & Polydispersibility Index

Formulation Code	Particle Size	PDI	Drug Content (%)
F1	62.80 nm	0.323	96.30
F2	137.90 nm	0.327	93.94
F3	104.60 nm	0.373	95.70
F4	117.00 nm	0.426	94.93

Table 6: Entrapment Efficiency

Formulation Code	EE%
F1	85.10
F2	81.32
F3	56.47
F4	72.83

Table 7: Physical Evaluation of Gel

Evaluation Parameters	F1	F2	F3	F4
Appearance	Transparent & Clear	Transparent & Clear	Transparent & Clear	Transparent & Clear
Colour	Pearl White	Pearl White	Pearl White	Pearl White
Odour	Charac-teristic	Charac-teristic	Charac-teristic	Charac-teristic
Consistency	Excellent	Excellent	Excellent	Excellent
Washability	Easily Wash	Easily Wash	Easily Wash	Easily Wash

Scanning Electron Microscopy (SEM)

The surface-developed NLC preparation's morphology was verified using SEM technology. Surface corrosion, flaws, contaminants, and fractures can all be found using high-resolution photos obtained from scanning electron microscopy (SEM) examination. Double-sided tape was used to secure a brass stub to a coverslip, and a drop of diluted NLC preparation was analysed using a scanning electron microscope. In order to make it electrically conductive, it was then dried and given a thin layer of gold. After that, the material was examined under a microscope to capture images [15].

DPPH Assay

Reagents: 0.3mM DPPH solution in ethanol. Standard solution of Resveratrol in ethanol (1mg/ml) was diluted to an annual conc. of 10, 20, 40, 60, 80 & 100µg/ml in ethanol. Standard soL. of Ascorbic Acid: Sample stock solution of Ascorbic acid in ethanol (1mg/ml) was diluted to an annual conc. of 10, 20, 40, 60, 80 & 100µg/ml in ethanol.

Procedure: Mix each 2mL sample extracts & 2mL DPPH (0.1mM) solution & stay it for 30min at dark place. Read mixture absorbance against a blank at 303nm by spectro-photometer. The activity of radical scavenging expresses the inhibition percentage (I%) which calculates by below formula.

Table 8: Physico-Chemical Evaluation of Gel

Evaluation Parameters	F1	F2	F3	F4
pH	6.74	6.85	7.04	6.96
Spreadability (g*cm/s)	21.13	24.97	27.10	23.91
Extrudability	83.35	90.12	91.86	83.94
Drug Content (%)	97.55	96.95	99.02	97.90
Viscosity (cp)	3800	4470	4600	4670

I (%) = (A Blank – A Sample/A Blank) *100

EC50 value (Expected conc. of sample which requires to 50% scavenge of free radical) is calculated via plot of inhibition (%) and concentration of Resveratrol. Each determination was made three times & average was noted. As standard antioxidants they use ascorbic acid [16].

Characterization of Resveratrol Loaded NLC Gel

Physical Evaluation: Physical characteristics including colour & uniformity were examined manually.

Wash ability: After applying the product by hand, it was examined under the flowing water.

Viscosity: A helipath stand-equipped Brookfield viscometer which used for calculating viscosity of various compositions. An LV-3 spindle rotating at 12 RPM was used to assess the viscosity of each formulation individually in triplicate after 50g of every formulation that transferred into individual beakers [17].

Spreadability/ Spread Capability: Spread capability was assessed by maintaining 0.5g of test formulation within 1cm diameter premarked circle on a glass plate. Shortly afterward, placed another glass plate on top of first & 500g of weight was let to rest for 5mins on the top glass plate. It was observed that the test formulation's diameter had changed [17].

S= M x L / T

Were,

S: Spread capability

M: Weight of material within pan

L: Glass slide's Length

T: Time (seconds) needed for slide to fully separate

Extrudability: Extrudability equipment was appropriately constructed in the laboratory. It was made up of a 45-degree-inclined hardwood block with a long, thin metal strip (tin) attached to one end, leaving the other end free. The wooden block with an angled surface was used to support the aluminium tube that held 15 grammes of gel. On the free end of the aluminium strip, a 1 kg weight was placed and lightly touched for 30 seconds. It was recorded how much gel was extruded from each tube [17].

pH: To measure the sample pH digital pH meter was used for testing of NLC-based gels shortly after it was calibrated using a reference buffer with pH values of 6.8 and 7.4 [17].

Drug content: Weigh a gramme of gel out in 100mL volumetric flask & dissolve it in methanol to remembering drug concentration. Then gel was adequately diluted & subjected to analysis by UV Visible Spectroscopy (Shimadzu UV-1800) at λ-max of 303nm [17].

In-vitro study of drug release: For in-vitro drug release investigation, Franz diffusion cell used with 7.4 pH solution of phosphate buffer in receptor compartment & 0.5gm of prepared gel in donor compartment. Franz diffusion cell's donor & receptor compartments are separated by egg membrane. Magnetic stirrer was used to mix gel & a 37 ˚C temperature was maintained. Solution of Phosphate buffer is used for maintaining the sink condition while sample was periodically removed. The samples were examined using UV spectroscopy at 303 nm [17].

RESULTS AND DISCUSSION

Preformulation Studies

Determining λmax

Absorption maximum of Resveratrol was found to be 303nm in phosphate buffer 7.4 pH and this wavelength was selected and utilized for further studies (Figure 1).

Calibration curve of Resveratrol

Table 3 shows the absorbance data of standard solutions. Absorbance value was plotted v/s respective concentrations (Figure 2). Concentration that shows linearity whenever curve was plotted which mentioned it follows Beers-Lambert Law. The values of the regression coefficient were

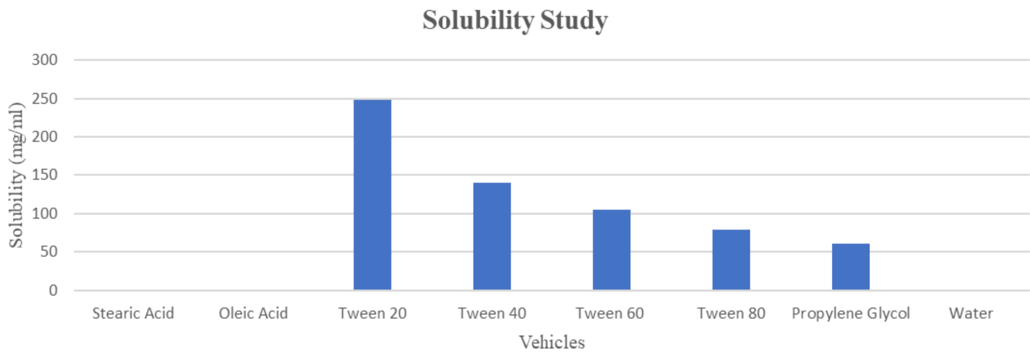

Figure 5: Graph of Solubility Study

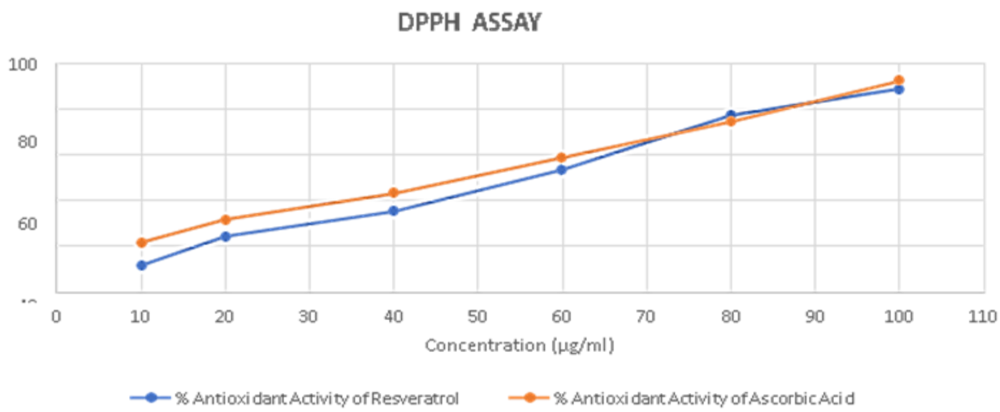

Figure 6: Graph of Antioxidant Activity (DPPH) Assay

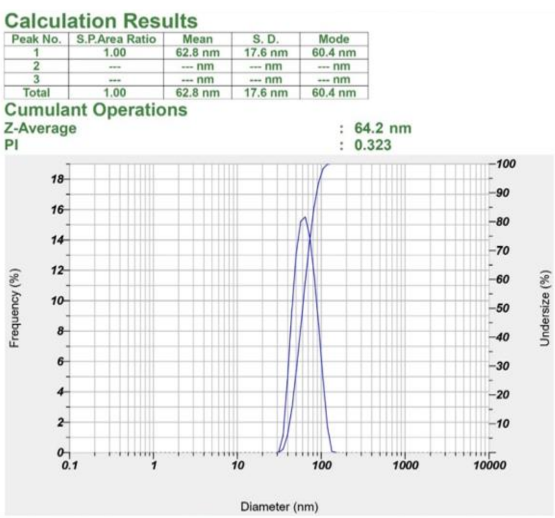

Figure 7: Globule Size and Polydispersibility Index of Formulation F1

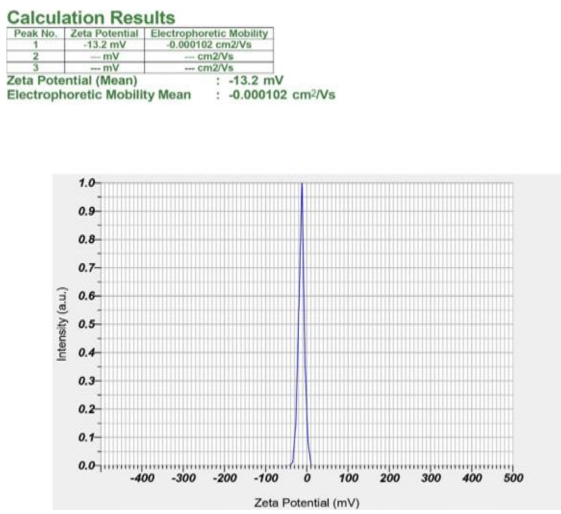

Figure 8: Zeta Potential of Formulation F1

Table 9: Percentage Cumulative Drug Release

Time (Hr)	% Cumulative Drug Release			
	F - 1	F - 2	F - 3	F - 4
0	0.0	0.0	0.0	0.0
1	13.73	19.99	14.60	22.25
2	36.33	27.60	30.64	30.15
3	39.51	42.67	43.78	44.82
4	48.14	51.82	55.60	54.41
5	54.16	58.19	64.60	65.42
6	61.58	69.63	71.83	74.24
7	71.69	75.78	81.37	81.62
8	81.83	82.95	93.84	91.82

0.9890 in 0.1N HCl, 0.9907 in phosphate buffer 6.8 & 0.9927 in phosphate buffer (pH 7.4).

Drug-Excipients Compatibility Studies

Fourier Transformed-Infrared (FT-IR) Spectroscopic Analysis

Compatibility study of API & Physical Mixtures was carried out using FTIR Spectroscopic Analysis (Figure 3). The results of FTIR Spectroscopic Analysis as follows.

API

Resveratrol showed significant bands at 3259.07 cm^{-1} for OH- stretch. The C-H bending was reported at 2928.17/cm. C=C & C-O bending was reported at 1584.61/cm & 1246.58/cm respectively. The C-H bending was reported at 830.10/cm.

Physical Mixture of NLC

The physical mixture showed significant bands at 2915.34/cm for C-H bending. C=C bending was reported at 1430.57/cm. C-O bending was reported at 1226.61. The C-H bending & C=C bending was reported at 688.90/cm & 1471.93/cm respectively.

Physical Mixture of Gel

The Physical Mixture demonstrated the distinct CH bending peak at 2922.47/cm. The C=C bending was reported at 1457.67/cm. C-O bending was reported at 1246.58/cm. OH-bending and CH-bending were reported at 1349.27/cm & 847.22/cm respectively.

Final Formulation NLC

The formulation of NLC containing drug Resveratrol, Tween 20, Stearic acid, oleic acid, and Propylene glycol shows significant peaks at 3343.22 cm^{-1} for OH- bending. The C-H stretch was reported at 2916.76/cm. The C=C and C-O bending was reported at 1459.09/cm & 1118.21/cm respectively.

Final Formulation of Gel

The formulation of Gel containing NLC, Sodium CMC, Methyl paraben, Propyl paraben, and Triethanolamine showed significant bands at 2851.01/cm for C-H bending. C=C bending was reported at 1457.67/cm. C-O bending was reported at 1223.76/cm. O-H bending and =CH & =CH2 bending were reported at 1412.03/cm & 938.50/cm respectively.

Differential Scanning Calorimetry

Thermal behaviours of (A) Pure Drug (B) NLCs physical Mixture (C) Physical Mixture of Gel, (D) Formulation of NLC and (E) Formulation of NLC Loaded Gel are shown in figure 4. DSC thermos-gram of Resveratrol shows characteristic endo-thermic peak at 235.60^{O}C. DSC thermogram of physical mixture of NLC containing Stearic acid, Oleic acid, Tween 20 & Propylene Glycol showed the characteristic peak at 237.40^{O}C. DSC analysis of physical mixture & pure drug of NLC states minimum change in M.P(melting point) of Resveratrol when it mixes with other excipients that indicates no drug-excipient interaction. DSC thermogram of physical mixture of gel containing Carbopol, Glycerine, Triethanolamine showed the characteristic peak at 233.20 ^{O}C. DSC analysis of physical mixture & pure drug of gel states minimum change in M.P(melting point) of Resveratrol when it mixes with other excipients that indicates no drug-excipient interaction. DSC thermogram of final formulation of NLCs and Final Formulation of Resveratrol Loaded NLC Gel shows Characteristic peak at 242.40 ^{O}C and 244.10 ^{O}C respectively. They show moderate change in M.P(melting point) of resveratrol when it mixes with other excipients that indicates some drug-excipient modification or interaction in the final formulation.

Determination of drug solubility in different oils, cosurfactants & surfactants

Solubility of Resveratrol in vehicles was screened & result are presented in figure 5. Among surfactant Resveratrol showed highest solubility in tween 20 (247.54 mg/ml). In Stearic Acid and Oleic Acid solubility of resveratrol was found to be 0.181mg/ml & 0.323mg/ml respectively. Solubility of Resveratrol in Propylene Glycol was found to be 60.74mg/ml. Therefore, Tween-20 was selected as surfactant based on solubility studies.

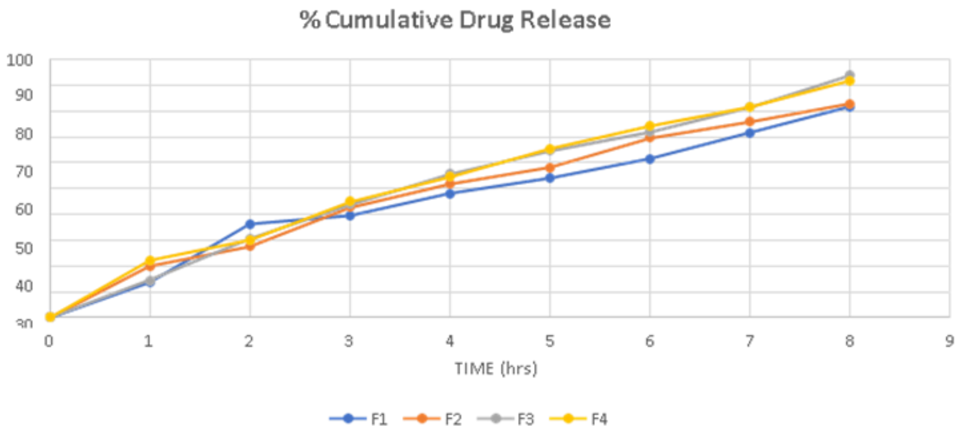

Figure 10: Graph of % Cumulative Drug Release

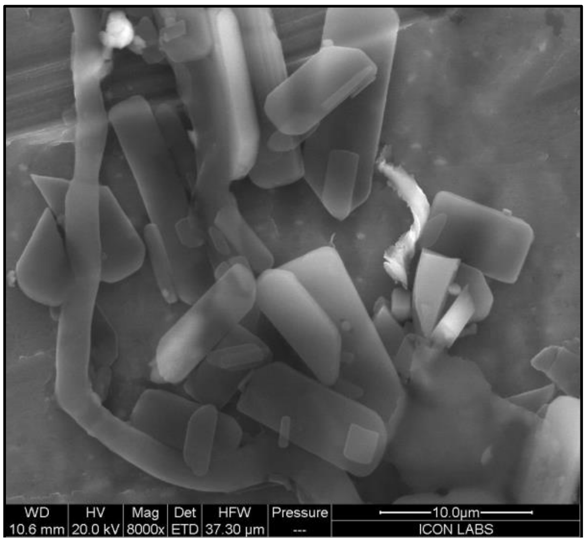

Figure 9: SEM of Formulation F1

DPPH Assay
Antioxidant activity of Resveratrol was carried out. The result of Antioxidant Activity of Resveratrol and Ascorbic Acid was displayed in Figure 6 & Table 4.

Characterization of Resveratrol Loaded NLCs

Determination of size of Globule & Polydispersibility Index
Result of size of Globule & Polydispersibility Index of optimized formulation was shown in Table 5 and Figure 7. The Globule size of the Resveratrol Loaded Nanostructured Lipid Carried was discovered in range of 62.80nm to 137.90nm and polydispersibility index in range of 0.323 - 0.426. The formulation F1 shows lowest globule size which is 62.80nm with polydispersibility index of 0.323. Less than 1 value of polydispersibility index indicates uniform distribution of droplets throughout the formulation.

Determining Zeta potential
Zeta potential value of optimized value of formulation F6 was dicsovered to be -13.2mV. Negative zeta potential value indicates the stable formulation. The result shown in figure 8.

Morphological Studies of Nano-structured Lipid Carrier by using SEM
SEM studies of Nanostructured Lipid Carrier states that Resveratrol presents in completely dissolved state into Nano-structured Lipid Carrier. SEM image of Nano-structured Lipid Carrier helps to conclude that particles are well separated & globular. However, non-uniform size is there (Figure8). The image of Nanostructured Lipid Carrier states that particles have small distribution of particle size having irregular surface area shown in (Figure 9).

Determining Entrapment Efficiency (EE)
Entrapment Efficiency of Resveratrol (Table 6) in Nano-structured Lipid Carrier was found between the range of 85.10 % - 72.83 %. Entrapment Efficiency value of optimized formulation F1 was found 85.10 %.

Characterization of Resveratrol Loaded NLC Gel Formulation:

Physical Evaluation of Gel Formulation
Physical Evaluations of gel was checked like Appearance, Colour, Odour, Consistency & Washability. Results of evaluations of the formulations are shown in Table 7.

Physico-Chemical Evaluation of Gel Formulation
The physicochemical parameters of gel were checked such as pH, content of drug, Spread capability, Extrudability, Viscosity & In-vitro release. Table 8 follows the results of physicochemical parameters of formulations.

In-vitro Drug Release
Table 9 lists formulations' % cumulative drug release. Graph of % Cumulative Drug Release are shown in figure 10.

CONCLUSTION

FTIR and DSC analyses of Resveratrol, Oleic acid, Tween 20, Stearic acid, and their physical mixture revealed no significant interactions. Loaded with resveratrol, solvent emulsification approach was utilized to create NLCs, with Tween 20 selected as the surfactant due to resveratrol's enhanced solubility compared to other surfactants. Size of particles, antioxidant activity (DPPH test), zeta potential, & entrapment efficiency were assessed in order to characterise the NLC formulations. Subsequently, NLCs remained incorporated into gel matrix by means of Carbopol 940 as the gelling agent. Resulting NLC-loaded gel formulations underwent preliminary assessments for appearance, color, odor, consistency, and washability. Furthermore, physicochemical parameters including pH, drug content, spreadability, extrudability, viscosity, & In vitro release kinetics in phosphate buffer (pH 7.4) were evaluated to comprehensively characterize the formulations.

REFERENCES

1. Gad, S.; fawzy, mohammed; adel, mohamed; Hamadi, T.; Ghourab, M. Nanostructured Lipid Carriers as Novel Drug Delivery System: A Review. *Rec. Pharm. Biomed. Sci.* 2023, *7* (3), 122–133. https://doi.org/10.21608/rpbs.2023.214962.1232.
2. Nagaich, U.; Gulati, N. Nanostructured Lipid Carriers (NLC) Based Controlled Release Topical Gel of Clobetasol Propionate: Design and in Vivo Characterization. *Drug Deliv. Transl. Res.* 2016, *6* (3), 289–298. https://doi.org/10.1007/s13346-016-0291-1.
3. Gu, Y.; Tang, X.; Yang, M.; Yang, D.; Liu, J. Transdermal Drug Delivery of Triptolide-Loaded Nanostructured Lipid Carriers: Preparation, Pharmacokinetic, and Evaluation for Rheumatoid Arthritis. *Int. J. Pharm.* 2019, *554*, 235–244. https://doi.org/10.1016/j.ijpharm.2018.11.024.
4. Phatak, A. A.; Chaudhari, P. D. Development and Evaluation of Nanostructured Lipid Carrier (NLC) Based Topical Delivery of an Anti-Inflammatory Drug. *J. Pharm. Res.* 2013, *7* (8), 677–685. https://doi.org/10.1016/j.jopr.2013.08.020.
5. Joshi, M.; Patravale, V. Nanostructured Lipid Carrier (NLC) Based Gel of Celecoxib. *Int. J. Pharm.* 2008, *346* (1–2), 124–132. https://doi.org/10.1016/j.ijpharm.2007.05.060.
6. Garg, N. K.; Sharma, G.; Singh, B.; Nirbhavane, P.; Tyagi, R. K.; Shukla, R.; Katare, O. P. Quality by Design (QbD)-Enabled Development of Aceclofenac Loaded-

Nano Structured Lipid Carriers (NLCs): An Improved Dermatokinetic Profile for Inflammatory Disorder(S). *Int. J. Pharm.* 2017, *517* (1–2), 413–431. https://doi.org/10.1016/j.ijpharm.2016.12.010.

7. Azhar, S. N. A. S.; Ashari, S. E.; Zainuddin, N.; Hassan, M. Nanostructured Lipid Carriers-Hydrogels System for Drug Delivery: Nanohybrid Technology Perspective. *Molecules* 2022, *27* (1). https://doi.org/10.3390/molecules27010289.
8. Astley, C.; Houacine, C.; Zaabalawi, A.; Wilkinson, F.; Lightfoot, A. P.; Alexander, Y.; Whitehead, D.; Singh, K. K.; Azzawi, M. Nanostructured Lipid Carriers Deliver Resveratrol, Restoring Attenuated Dilation in Small Coronary Arteries, via the AMPK Pathway. *Biomedicines* 2021, *9* (12). https://doi.org/10.3390/biomedicines9121852.
9. Shirsath, N. R.; Goswami, A. K. Nanocarriers Based Novel Drug Delivery as Effective Drug Delivery: A Review. *Curr. Nanomater.* 2019, *4* (2), 71–83. https://doi.org/10.2174/2405461504666190527101436.
10. Gao, S.; Tian, B.; Han, J.; Zhang, J.; Shi, Y.; Lv, Q.; Li, K. Enhanced Transdermal Delivery of Lornoxicam by Nanostructured Lipid Carrier Gels Modified with Polyarginine Peptide for Treatment of Carrageenan-Induced Rat Paw Edema. *Int. J. Nanomedicine* 2019, *14*, 6135–6150. https://doi.org/10.2147/IJN.S205295.
11. Patel, D.; Dasgupta, S.; Dey, S.; Roja Ramani, Y.; Ray, S.; Mazumder, B. Nanostructured Lipid Carriers (NLC)-Based Gel for the Topical Delivery of Aceclofenac: Preparation, Characterization, and in Vivo Evaluation. *Sci. Pharm.* 2012, *80* (3), 749–764. https://doi.org/10.3797/scipharm.1202-12.
12. Ilyas, U.; Asif, M.; Wang, M.; Altaf, R.; Zafar, H.; Faran Ashraf Baig, M. M.; Paiva-Santos, A. C.; Abbas, M. Nanostructured Lipid Carrier-Based Delivery of Pioglitazone for Treatment of Type 2 Diabetes. *Front. Pharmacol.* 2022, *13*. https://doi.org/10.3389/fphar.2022.934156.
13. Joshi, M.; Patravale, V. Formulation and Evaluation of Nanostructured Lipid Carrier (NLC)-Based Gel of Valdecoxib. *Drug Dev. Ind. Pharm.* 2006, *32* (8), 911–918. https://doi.org/10.1080/03639040600814676.
14. Rincón, M.; Calpena, A. C.; Fabrega, M. J.; Garduño-Ramírez, M. L.; Espina, M.; Rodríguez-Lagunas, M. J.; García, M. L.; Abrego, G. Development of Pranoprofen Loaded Nanostructured Lipid Carriers to Improve Its Release and Therapeutic Efficacy in Skin Inflammatory Disorders. *Nanomaterials* 2018, *8* (12). https://doi.org/10.3390/nano8121022.
15. Agrawal, Y. O.; Mahajan, U. B.; Mahajan, H. S.; Ojha, S. Methotrexate-Loaded Nanostructured Lipid Carrier Gel Alleviates Imiquimod-Induced Psoriasis by Moderating Inflammation: Formulation, Optimization, Characterization, in-Vitro and in-Vivo Studies. *Int. J. Nanomedicine* 2020, *15*, 4763–4778. https://doi.org/10.2147/IJN.S247007.
16. Govindarajan, R.; Rastogi, S.; Vijayakumar, M.; Shirwaikar, A.; Rawat, A. K. S.; Mehrotra, S.; Pushpangadan, P. Studies on the Antioxidant Activities of Desmodium Gangeticum. *Biol. Pharm. Bull.* 2003, *26* (10), 1424–1427. https://doi.org/10.1248/bpb.26.1424.
17. Palei, N. N.; Mohanta, B. C.; Das, M. K.; Sabapathi, M. L. Lornoxicam Loaded Nanostructured Lipid Carriers for Topical Delivery: Optimization, Skin Uptake and in Vivo Studies. *J. Drug Deliv. Sci. Technol.* 2017, *39*, 490–500. https://doi.org/10.1016/j.jddst.2017.05.001.