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Original Article

Formulation and Evaluation of Simvastatin Loaded Nanostructured Lipid Carrier for Topical Drug Delivery

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ABSTRACT

Introduction: Simvastatin, a BCS II drug, has poor water solubility and low bioavailability. Nanostructured Lipid Carriers (NLCs) can enhance its bioavailability. This study investigates the potential of NLCs to improve simvastatin's bioavailability. **Objectives:** The primary objective was to enhance simvastatin's bioavailability by formulating it into NLCs using High-Speed Homogenization (HPH). The study also aimed to characterize the NLCs and evaluate their stability and irritation potential. **Materials and Methods:** Simvastatin-loaded NLCs were prepared with Compritol 888 ATO, oleic acid, linseed oil, Tween 80 and distilled water using high-speed homogenization. Characterization included FTIR, DSC and PXRD. The optimized batch (F-II) was assessed for entrapment efficiency, particle size, polydispersity index, zeta potential and drug content. Stability and irritation potential were evaluated following ICH guidelines and Primary Irritation Index (PII) assessment. **Results:** FTIR showed no drug-excipient interactions. XRD confirmed the amorphous nature of simvastatin in NLCs. The optimized batch (F-II) had 78% EE, 148.4 nm particle sizes, 0.369 PDI, -2.90 mV ZP and 89.6% drug content. Stability studies confirmed robustness and PII was 0.11, indicating negligible irritation. **Conclusion:** HPH successfully prepared simvastatin-loaded NLCs, significantly enhancing bioavailability with favorable %EE, particle size and drug content. The formulation was stable and showed minimal irritation potential, making NLCs optimistic techniques for improving the bioavailability of poorly soluble drugs like simvastatin.

Keywords: Nanostructured Lipid Carrier, High-Speed Homogenization, Compritol 888 ATO.

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INTRODUCTION

Several obstacles prevent drugs from entering the systemic circulation, making a conventional approach to drug administration continuously difficult to provide effective dosage forms. The *in vivo* pharmacological responses are severely limited by challenges like poor drug solubility and absorption, reduced bioavailability because of rapid first-pass metabolism, fluctuations in plasma drug concentrations and interactions with food. These issues frequently leading in the direction of the failure of conventional Drug Delivery Systems (DDS).[1] In the realm of drug delivery research, nanotechnology has emerged as a transformative force, offering unprecedented precision in controlling nanoparticle characteristics such as size, shape and composition. Among the various avenues of exploration, lipid-based drug carriers have garnered considerable attention for their adaptability and potential applications across diverse therapeutic domains.

NLCs representing a cutting-edge progression within the realm of Solid Lipid Nanoparticles (SLNs) and offer an optimistic substitute in the direction of conventional DDS like solutions, ointments and suspensions[2]. NLCs consist of a solid lipid mixed with a liquid lipid, strategically designed to address challenges such as the high crystallinity of the lipid matrix and drug leakage throughout storage, which are often encountered with SLNs. NLCs represent the pinnacle of lipid nanoparticle technology, surpassing their predecessors with improved drug loading capacity, stability and controlled release characteristics. Their versatility extends across pharmaceuticals, clinical medicine and allied sciences, positioning them as pivotal players in the pharmaceutical landscape.[1,2]

Lipid nanoparticles, including NLCs, offer distinct advantages over other nanoparticulated DDS, boasting high biocompatibility and adaptability for various administration routes such as topical,

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oral, pulmonary and parenteral delivery. Their security profile and effectiveness make them attractive not only for pharmaceuticals but also for vaccines, diagnostics and Nutraceuticals. With their unique blend of solid and liquid lipids, NLCs provide a flexible matrix that enables higher drug loading and controlled release, addressing critical challenges in pharmaceutical formulation. Their small size and uniform distribution facilitate targeted drug delivery and protect drugs from degradation, further enhancing their appeal in therapeutic interventions.[3]

Furthermore, the development of NLCs holds promise in topical DDS, particularly for increasing skin penetration and drug delivery efficiency.[4] These carriers offer advantages such as increased skin hydration, chemical stability of incorporated compounds and sustained release profiles, making them Optimistic candidates for various dermatological and cosmetic applications. However, despite significant progress, there remains a need for further research to optimize formulations and address specific challenges associated with drug targeting, stability and efficacy.[5-7]

Simvastatin, an HMG CoA reductase inhibitor, reduces LDL and TG levels while increasing HDL, lowering cardiovascular risk. However, simvastatin presents challenges in its pharmacokinetic profile, including a low bioavailability of 5%, extensive protein binding capacity of 95% and hepatic metabolism primarily mediated by CYP3A4, resulting in a notably short biological half-life of just 2 hr. However, its low bioavailability, high protein binding, hepatic metabolism via CYP3A4 and short half-life pose challenges.[8-13] Utilizing NLCs in transdermal patches offers an optimistic solution to enhance simvastatin's delivery, potentially improving its efficacy and therapeutic outcomes.

MATERIALS AND METHODS

Materials

Simvastatin USP was acquired from Emcure, Pune, while Glyceryl monostearate was procured from Sigma-Aldrich. Compritol 888 ATO was gained from Gattefosse India, Mumbai. Oleic acid and Tween 80 were acquired from Loba Chemie Pvt. Ltd., Linseed oil was provided by Fame drugs and methanol was supplied by Merck Chemicals. All chemicals used were of analytical grade.

Methods

Development of nanostructured lipid carrier dispersion

HPH techniques were used for NLC formation. The drug was dissolved in a liquid lipid; the solid lipids were heated up to 70°C and allow melting completely. In aqueous phase, stabiliser was dissolved and its temperature was sustained at the similar temperature of lipid solution. The stabiliser solution was slowly additional in to lipid phase followed by homogenization at about 15,000 rpm and sonication for approximately 10 min. Afterward, the mixture was cooled to RT, resulting in the formation of NLC dispersion.[8,9] The developed NLC dispersions were stored at 25°C until used further. The trial batch compositions are in Tables 1 and 2.

Formulation of NLC gel

The optimized NLC dispersion was integrated into an NLC gel formulation. Carbopol 934 (2%) was introduced to the optimized batch of NLC dispersion while employing overhead stirring at 800 rpm until complete dispersion of Carbopol was achieved. Neutralization of the Carbopol dispersion was carried out using 0.05% (w/w) triethanolamine and the pH was subsequently adjusted to 6.[14-19]

Evaluation of nanostructured lipid carrier dispersion

Determination of entrapment efficiency

A suspension containing SMV loaded NLCs (1 mL) was ultra-centrifuged at 80,000 rpm for 1 hr. Following centrifugation, the supernatant was carefully separated from the pellets and the drug concentration in both fractions was calculated spectrophotometrically at 238 nm. Entrapment efficiency was then calculated using the provided equation.[20]

$$Entrepatment\ efficiency = \frac{Amount\ of\ drug\ in\ NLC\ (Ct-Cf)}{Amount\ of\ drug\ incorporated\ in\ formulation} \times 100 \text{------- (1)}$$

Where,

Ct is concentration of total drug in formulation,

Cf is concentration of free drug (Unentrapped).

% Drug content

SMV loaded NLC dispersion (1 mL) was mixed in 10 mL methanol and dissolved properly. The resulting dispersion was sonicated for few minutes and filtered. Dilutions were made as per requirement. Analysis was carried out by using spectrophotometer at 238 nm. The % drug content can be calculated using formula.[21]

$$\%\ Drug\ content = \frac{Amount\ of\ drug\ obtained\ actually\ present}{Theoretical\ drug\ load\ expected} \times 100 \text{------ (2)}$$

Particle size analysis

A 1 mL sample of SMV loaded NLC was diluted with purified water (H_2O) to achieve a final concentration of 5% v/v. The average particle size of this dispersion was then measured using a particle size analyser (NANOPHOX- NX0088).[20,21]

Zeta Potential (ZP) and Polydispersity Index (PDI)

SMV loaded NLC dispersion (0.5 mL) was diluted to 5 mL with double purified H_2O and samples were analysed in Malvern Zeta sizer to get the ZP and PDI.[10,11]

Stability studies

The accelerated stability study, conducted per ICH recommendations, involved storing optimized NLC dispersions

in sealed amber glass vials for 3 months. Drug content was analysed at the study's end.[12,13]

Evaluation of NLC gel

Homogeneity

The homogeneity of the developed gel was calculated by visually and inspected for appearance and aggregates.[15]

Grittiness

Microscopic evaluation found no significant particulate matter under a light microscope, confirming the gel formulation meets the requirement of being free from particles and grittiness, as expected for a topical formulation.[16]

Determination of pH

The pH of the NLC gel preparation was assessed using a digital pH meter. 1 g of gel was softened in 100 mL of purified H_2O for triplicate pH measurements, with average results recorded for accuracy.[17]

Drug content

A 500 mg of Simvastatin loaded NLC gel was melted in 10 mL of methanol and subjected to 2 hr of sonication for complete dissolution. After appropriate dilution, the solution was filtered through Whatman filter paper and drug content was analysed by spectrophotometer at 238 nm.[18]

Rheological Studies

The viscosity and rheological characteristics of the gel preparations were assessed using a cone and plate viscometer at a controlled temperature of 25±1°C. Spindle CP52 was used at various speeds for the measurements.[19]

Spreadability

The spreadability of the gel was evaluated using the Brookfield texture analyser. The parallel plate techniques commonly employed for assessing and quantifying the spreadability of semi-solid.

In vitro Drug release

To replicate the skin barrier, the cellophane membrane was soaked in pH 7 buffer for two hr prior to the experiment. For the *in vitro* diffusion tests of the produced gels, a hollow tube diffusion cell was used with a receptor compartment containing a pre-soaked cellophane membrane and buffer at pH 7 (17 mL). The gel formulation (2 g) was evenly applied onto the membrane. The donor and receptor sections were in contact at 37±0.5°C, with stirring on the receptor side using a magnetic stirrer. At specified intervals, 2 mL of receptor fluid was taken up and exchanged with fresh pH 7 buffers. The sample (2 mL) was diluted with 2 mL of methanol and analysed spectrophotometrically at 238 nm to determine drug concentration.[22-24]

In vivo animal study

The anti-inflammatory potential of the simvastatin gel was evaluated using the carrageenan-caused left hind paw edema technique. Acute inflammation was caused by injecting 0.1 mL of 1% carrageenan suspension into the left hind paw of rats. 1 hr after applying the gel trans dermally, paw volume was measured using a plethysmometer at 0, 1, 2, 3, 4, 5, 6, 7 and 8 hr post-injection.[24-26]

RESULTS

Evaluation of NLCs dispersion

The NLC of SMV was evaluated for physicho-chemical properties. All evaluation parameters are represented in Table 3.

Entrapment efficiency (%EE)

The % drug EE in SMV-loaded NLC was analysed at 238 nm using a UV spectrophotometer. Formulation II showed 78% EE, while formulation B exhibited 76%. At the same time 68.5% for the formulation C. Figure 1 shows the comparative EE of all the NLC batches.

Table 1: Composition of trial batches with Compritol 888 ATO.

Batch code	Drug (mg)	Compritol 888 ATO (mg)	Oleic acid (mg)	Linseed oil (mg)	Tween 80 (%)	Water (mL)
I	100	160	30	-	1.5	25
II	100	160	50	-	1.5	25
III	100	160	-	30	2	25
IV	100	160	-	50	2	25

Table 2: Composition of trial batches with GMS.

Batch code	Drug (mg)	GMS (mg)	Oleic acid (mg)	Linseed oil (mg)	Tween 80 (%)	Water (mL)
A	100	100	50	-	1.5	25
B	100	200	100	-	1.5	25
C	100	100	-	50	2	25
D	100	200	-	100	2	25

Drug content

The drug content of SMV-loaded NLC was analyzed at 238 nm using a UV spectrophotometer. Formulation I showed a drug content of 89.6% and formulation B exhibited 88.8%. At the same time 75.2% for the formulation C. Figure 2 shows the comparative drug content of all the NLC batches.

Particle size distribution

The particle size distribution data is illustrated in Table 3 and Figure 3.

The Figure 3 represents PSD of formulation batches of simvastatin loaded NLC in liquid dispersion after further processing. From the graph, it was observed that formulation II and formulation B has shown the minimum particle size i.e. 148.4 nm and 180.7 nm respectively. Where, formulation IV and C has shown the maximum i.e. 628.3 nm and 503.1 nm respectively. The particle size of the batch II is presented graphically in Figure 4.

Zeta potential

Table 3 presents the ZP of simvastatin-loaded NLC formulations in liquid dispersion after processing. ZP, critical for assessing NLC dispersion stability, reflects particle surface charge and the repulsion amongst similarly charged particles, preventing aggregation. The ZP of the batch II is presented graphically in Figure 5.

Polydispersity Index (PDI) of NLC

The PDI of all batches was found to be less than one, indicating a uniform particle size distribution in the samples. The Table 3 represents PDI of formulation batches of simvastatin loaded NLC in liquid dispersion after further processing. Polydispersity index of formulation batches of simvastatin loaded NLCs is less than 0.7 therefore type of dispersion is mid-range polydisperse.

Stability studies (NLC Dispersion)

Table 4 presents the findings from stability investigations.

Evaluation parameters of NLC gel

Homogeneity and Grittiness

The optimized NLC gel formulations II and B were free of grittiness, homogeneous and showed no phase separation.

pH of the formulation

Formulations II and B have pH values of 6.34 and 6, respectively, which are within the skin's typical pH range and unlikely to cause irritation.

Viscosity of the formulation

The viscosity of the NLC gels at various rpm is given in Table 5. The viscosity of the formulation II and B at increasing RPM is presented graphically in Figure 6.

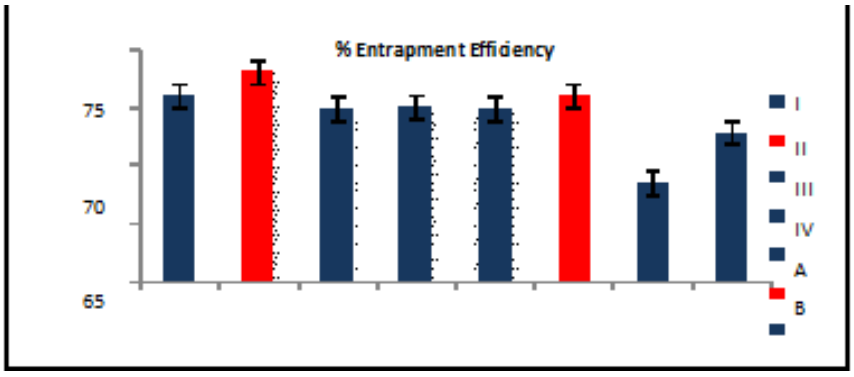

Figure 1: Comparative EE of SMV form different NLC formulations.

Table 3: Evaluation of batches *in vitro*.

Batch Code	(%) EE	(%) Drug Content	Particle Size (nm)	ZP (mV)	PDI
I	76	87.22	212.9	-0.757	0.355
II	78	89.6	148.4	-2.90	0.369
III	74.8	87.4	218.9	-1.39	0.321
IV	75	77.6	628.3	-5.39	0.863
A	74.8	82.4	196.6	-4.36	0.524
B	76	88.8	180.7	-6.16	0.433
C	68.5	75.2	503.1	-6.91	0.618
D	72.8	83.2	240.7	-6.95	0.643

Spreadability

In case of NLC gel- II, the adhesive force was found to be 554 g and adhesiveness was found to be 13.90 mJ, NLC gel- B, the adhesive force was found to be 260 g and adhesiveness was found to be 10.50 mJ. The spreadability results are presented graphically in Figures 7 and 8.

Drug content

The drug content of NLC gel formulations II and B was determined to be 85.4% and 86.8%, respectively.

In vitro drug diffusion study

Drug diffusion was assessed according to the experimental procedure outlined. The drug diffusion pattern is presented in Table 6 and Figure 9.

Stability studies of NLC gel

The accelerated stability study was conducted following ICH guidelines at 40ºC/75% RH to evaluate drug content and pH of NLC gel formulation. After 90 days, formulations II and B showed drug contents of 82.9% and 83.2%, respectively, with pH values measured at 6.12 and 6.

Skin irritation study

The scores for erythema and edema following the application of simvastatin NLC gel to rats are presented in Table 7 and Figure 10.

Anti-inflammatory activity

Details of animal grouping and treatment are provided in Table 8.[27]

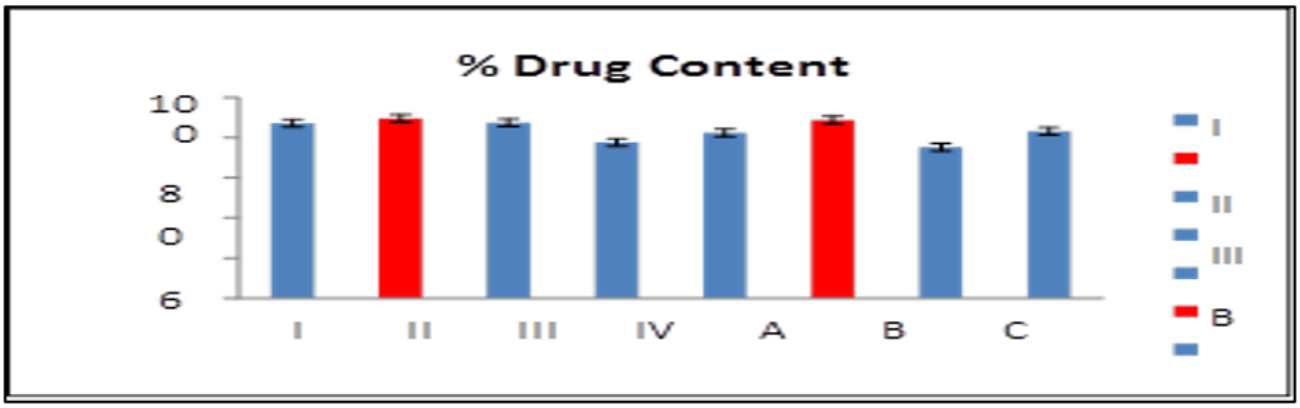

Figure 2: Graphical representation of % Drug Content.

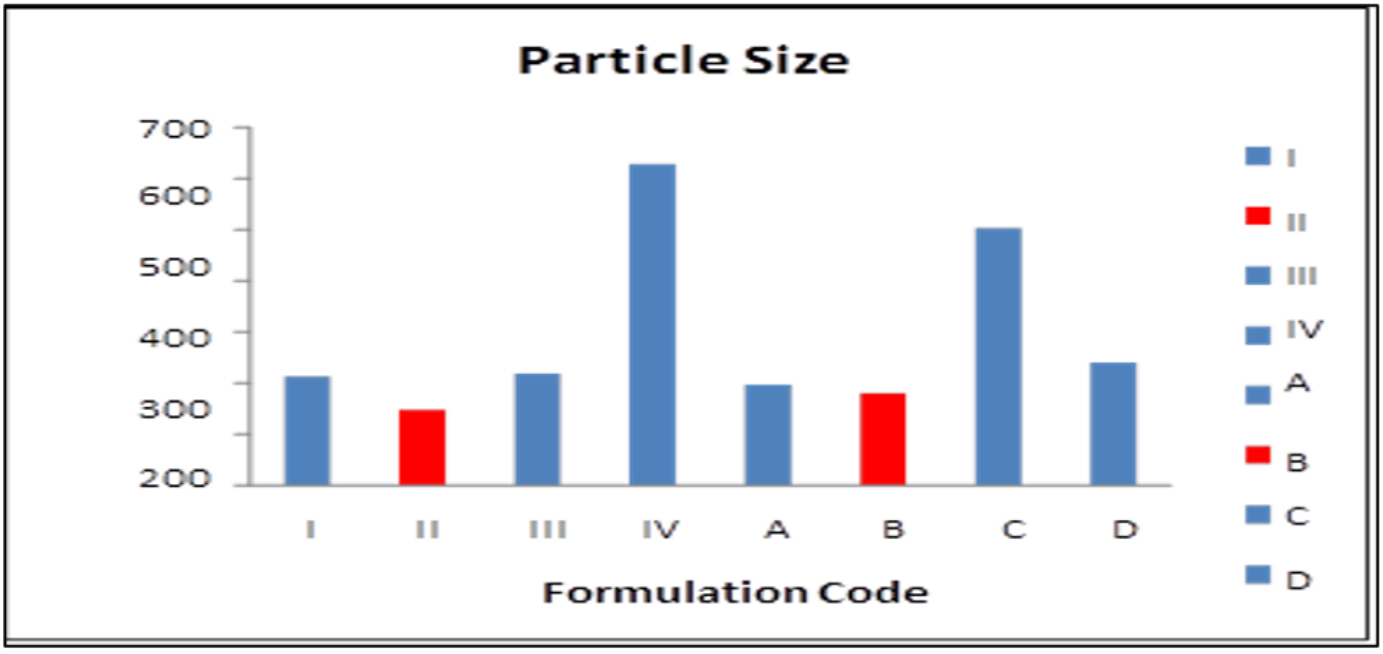

Figure 3: Graphical representation of Particle size.

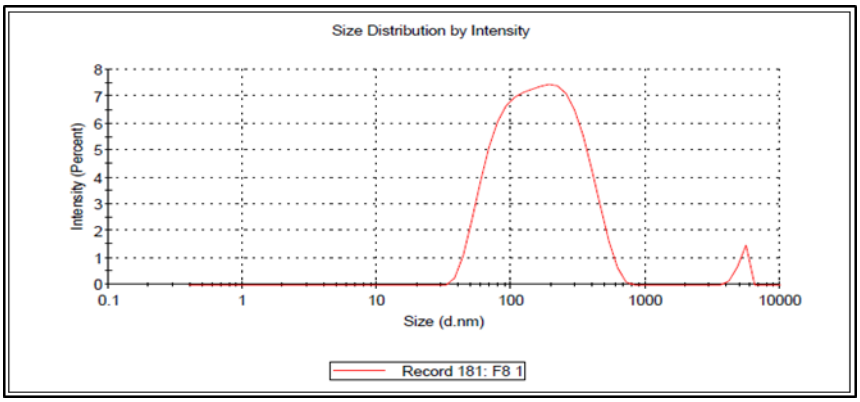

Figure 4: Image of average particle size of NLC 148.4 nm of batch II.

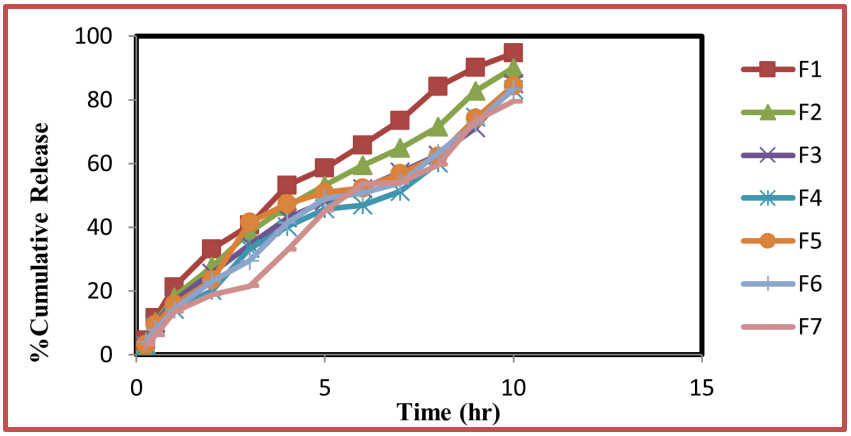

Figure 5: presenting the value of zeta potential of NLC - 2.90mV of batch II.

Table 4: Stability study (40°C/75% RH).

Time (Days)	Drug Content	
	NLC Formulation- II	NLC Formulation- B
30	84.8	86.12
60	84.1	85.3
90	83.6	84.2

Prior to the experiment, the animals were accommodated in a facility through accessing toward sufficient food and water. They were then separated into four groups: control, standard, test I and test II, each consisting of six animals. Following administration, paw volume was measured at specified intervals using a plethysmometer (VJ Instrument, Nagpur) for all groups. The findings of carrageenan-caused paw edema are detailed in Table 9 and depicted in Figure 11.

The percentage inhibition of paw volume, indicating the reduction in edema, for the two optimized NLC gels was approximately 59.40% for NLC Gel II and 55.64% for NLC Gel B in Table 10 and Figure 12.

DISCUSSION

NLCs have gained significant attention in topical drug delivery due to their unique ability to enhance drug stability, improve skin penetration and provide controlled release of active ingredients. NLCs consist of a mixture of solid and liquid lipids, offering a highly structured matrix that can encapsulate lipophilic drugs like simvastatin effectively. This lipid matrix not only protects the drug from degradation but also improves its solubility and bioavailability when applied to the skin. The small particle size and high surface area of NLCs facilitate closer contact with the skin, improving drug permeation and retention in the targeted area, which is crucial for achieving therapeutic efficacy in topical applications.

In this study, the transformation of simvastatin-loaded NLCs into a gel form was explored to address common limitations associated with conventional topical formulations, such as low viscosity and short residence time on the skin. By enhancing the viscosity, the NLC gel ensures prolonged retention at the application site, allowing for sustained drug release and more effective management of inflammation. These characteristics justify the selection of NLCs for simvastatin delivery, as they not only enhance the drug's stability and absorption but also provide a formulation that is more suitable for practical use in topical

therapies. The results of this study demonstrate the potential of NLCs to deliver simvastatin effectively through the skin, offering a promising approach for improving therapeutic outcomes in the treatment of inflammatory conditions.

There are several techniques for formulation of NLC but after going through the aspects of literature survey it was concluded that HPH techniques is suitable techniques for formulation of NLC because, this technique is economical and easy as in comparison with supplementary techniques of preparation of NLC. This technique has numerous benefits over other techniques for example a smaller number of ingredients are required, ease of preparation, less cost required for formulation and devoid of any volatile solvent.[6,7] Compritol 888 ATO and glyceryl Monostearte was selected as solid lipid whereas oleic acid and linseed oil as liquid lipid and tween 80 was selected as stabilizer for formulation of NLC.[27] In trial batches homogenization speed was varied as 8000 rpm, 10,000 rpm and at 14000 rpm for 5 and 10 cycles of 1 min each. From the result it was observed that 10,000 rpm and 10 cycles were suitable to produce NLC with uniform size.[28]

Evaluation of NLCs dispersion

Depending on the %EE formulation was selected for further studies.[29,30] From the Figure 1 it was observed that, formulation

Table 5: Viscosity of NLC gel- II, NLC gel- B at various rpm.

Sl. No.	RPM	Viscosity (Centipoise)	
		NLC gel- II	NLC gel- B
1	10	5760±4	8064±5.6
2	20	3456±3.2	4864±5.5
3	30	2773±4.5	3157±4
4	40	2496±3	2560±3
5	50	2022.7±3.5	2048±3
6	60	1536±3	2005.7±4
7	70	1408.7±3.1	1737±2.5
8	80	1328±4	1488±5.6
9	90	1166±3.6	1351.7±2.5
10	100	1050±2.6	1216±2.6

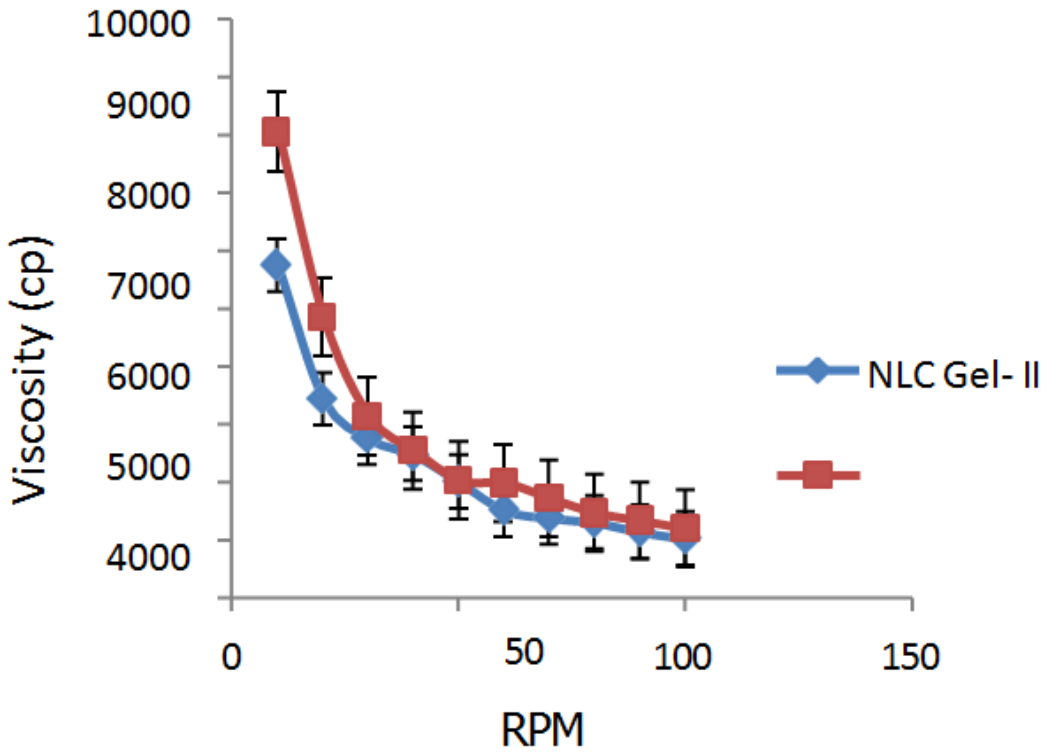

Figure 6: Viscosity of NLC gel- II and NLC gel- B at various RPM.

II and formulation B has shown maximum %EE and at the same time formulation C has shown minimum EE. Depending on the drug content formulation was selected for further studies.[31] From the Figure 2 it was observed that, formulation II and formulation B has shown maximum drug content and at the same time formulation C has shown minimum drug content. The PSD data represents particle size distribution of formulation batches of simvastatin loaded NLC in liquid dispersion after further processing. The mean diameter for formulation II was found to be 148.4 nm and for formulation B was 180.7 nm. Thus, all the particles were found to be uniform in size.[32] All the particles were uniform in size. This uniform particle size distribution may be attributed to increased supersaturation, which enhances nucleation and inhibits crystal growth.[33] Higher ZP values (>+20mVor<-20mV) indicate strong electrostatic repulsion, ensuring greater stability. Accordingly, illustration from the information provided in Table 3, it is evident that the prepared formulations exhibit favourable physical stability.[34] In all batches ZP was found within acceptable range. PDI assesses how molecular mass is distributed in a polymer sample, indicating the range of individual molecular masses within a batch. It is derived from the mean diameter and signifies the scope of particle size distribution. A subordinate PDI specifies uniform particle sizes (monodisperse), while a higher PDI indicates greater variability in particle sizes (polydisperse). The PDI calculated by following equation.[34,35]

$$PDI = \frac{\Delta d}{dvag} \text{---------- (3)}$$

Accelerated stability study was performed on formulation II and B. It was observed that in drug content of optimized NLC formulation- II and formulation- B there was no significant change observed.[25,36]

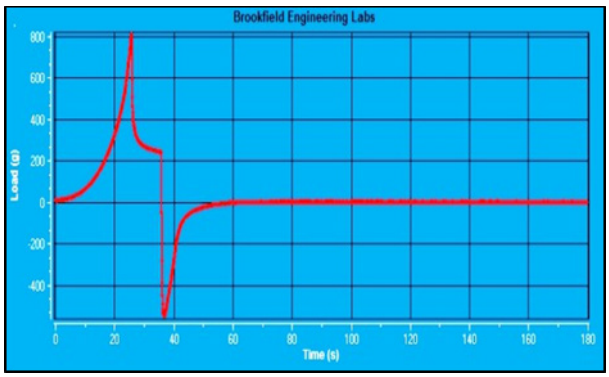

Figure 7: Spreadability Study of NLC gel-II.

Table 6: ***In vitro*** **drug diffusion of NLC gel-II and NLC gel-B.**

Time	NLC Gel- II	NLC Gel- B
30	11.92±0.26	9.53±0.52
60	21.45±0.24	11.2±0.43
120	24.63±0.34	13.5±0.54
180	27.8±0.28	18.27±0.23
240	30.19±0.29	25.42±0.34
300	32.57±0.8	30.98±0.39
360	30.93±0.6	33.36±0.41
420	42.9±0.28	38.93±0.32
480	54.81±0.32	41.31±0.26

Evaluation parameters of NLC gel

The developed NLC gel were found to be white, viscous, creamy consistency with a smooth, homogeneous texture and a glossy appearance.[21,37,38] The pH of the gel was found to be compatible with skin due to the inclusion of triethanolamine, which was mixed into the final gel to neutralize the acidic groups in the polyacrylate chains of the carbopol polymer. The pH values for the NLC gel formulations remained stable over time.[19,20] The viscosity of the both formulations was found to be decreasing

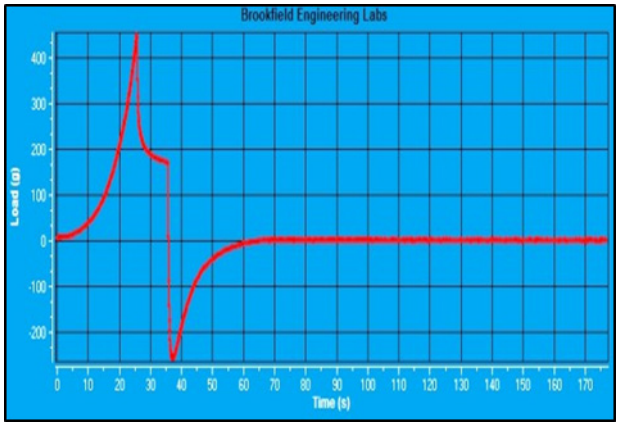

Figure 8: Spreadability Study of NLC gel-B.

Table 7: **Results of erythema and edema.**

Rat No.	Reactions	Test group I			Test group II			Control group		
		24 hr	48 hr	72 hr	24 hr	48 hr	72 hr	24 hr	48 hr	72 hr
1.	Erythema	0	1	1	0	1	1	0	0	0
	Edema	0								
2.	Erythema	0								1
	Edema	0								
3.	Erythema	0								
	Edema	0								

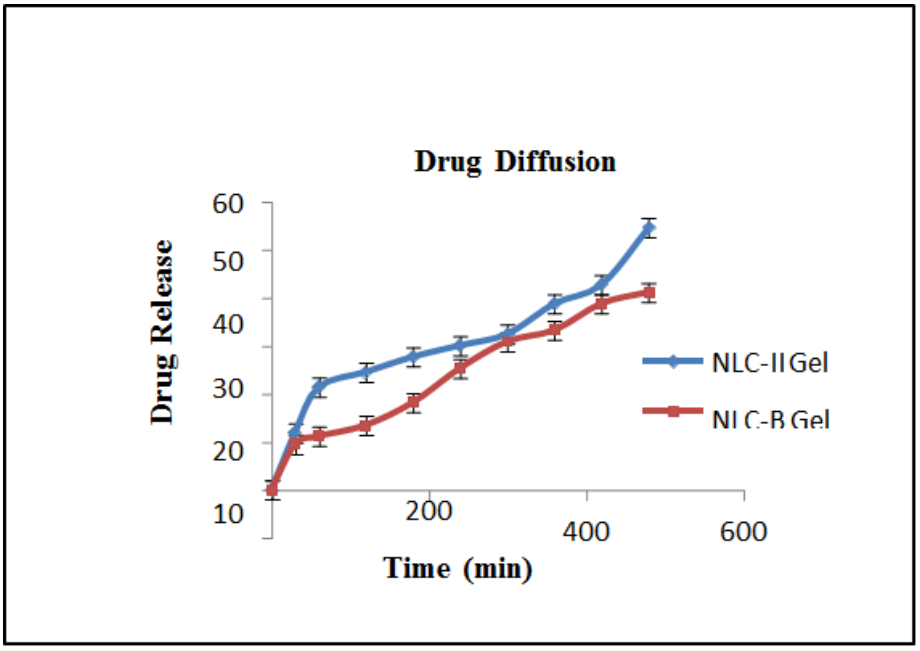

Figure 9: *In vitro* drug diffusion of NLC gel- II and NLC gel- B.

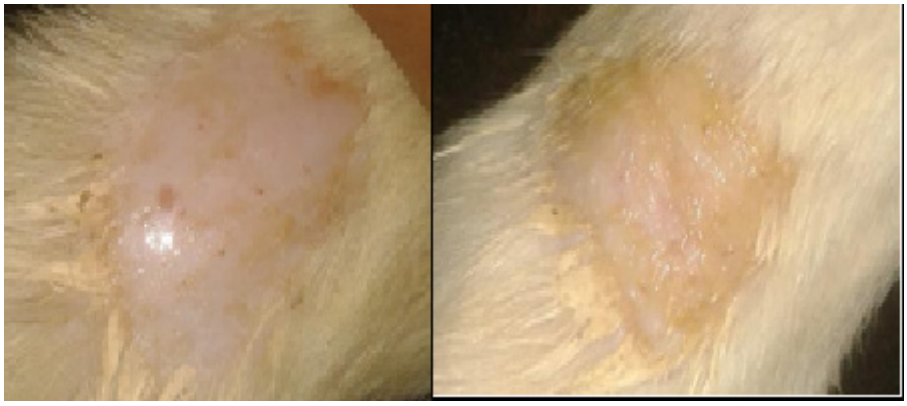

Figure 10: Skin irritation study.

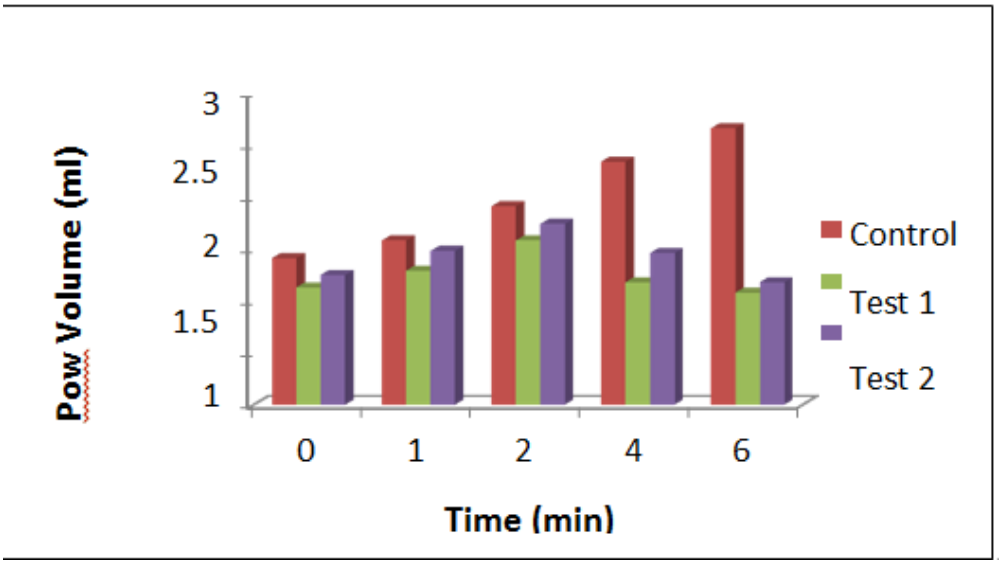

Figure 11: Graphical representation of paw volume in rat.

Table 8: ***In vivo*** **Anti-inflammatory activity of optimized formulation.**

Group	Animals	Treatment
Control	06	Normal saline
Test I	06	NLC gel- II
Test II	06	NLC gel- B

Table 9: Outcomes of *in vivo* anti-inflammatory activity

Exp. group	Paw volume (mL)				
	0 min	1 hr	2 hr	4 hr	6 hr
Control	1.41±0.09	1.58±0.13	1.91±0.15	2.34±0.10	2.66±0.17
Test I	1.13±0.05	1.29±0.08	1.58±0.07	1.18±0.09	1.08±0.03
Test II	1.25±0.15	1.48±0.12	1.74±0.13	1.46±0.18	1.18±0.05

Table 10: % Inhibition of inflamed paw volume in carrageenan caused paw edema in rats.

Group	% Inhibition Paw Volume				
	0 min	1 hr	2 hr	4 hr	6 hr
Test I	0.88	18.35	17.28	49.57	59.40
Test II	0.65	6.33	8.90	37.61	55.64

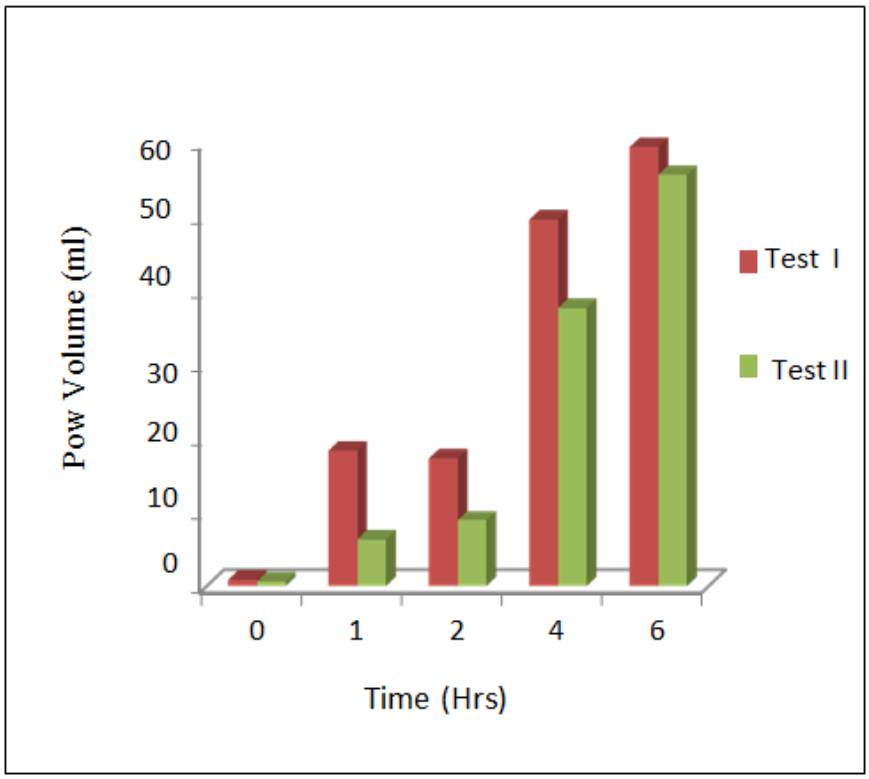

Figure 12: Graphical representation of % Inhibition Paw Volume in rat.

with increase in RPM. The results of the spreadability studies indicated that the spreading area decreased as viscosity increased, demonstrating the inverse relationship between spreadability and viscosity. *In vitro* diffusion study showed that 54.81% of the drug diffused within 8 hr for NLC gel II, while 41.31% of the drug diffused for NLC gel B.[22,39] The accelerated stability study reveled no notable alterations in drug content, appearance, pH, or viscosity throughout storage, confirming the stability of the NLC gels under these conditions.[31,35,36] The Primary Irritation Index (PII) was determined to be 0.11 for both test groups, falling within the acceptable range of 0-0.4, indicating negligible irritation. The optimized formulation was tested for its anti-inflammatory effects using female Wistar rats from a local strain. The study

employed the carrageenan-caused rat paw edema model to evaluate anti-inflammatory activity.

CONCLUSION

NLCs are widely used for delivering drugs and cosmetics through the skin. However, NLC dispersions typically have low viscosity, which limits their effectiveness in topical applications due to reduced residence time at the application site. To address this, in our study, we transformed simvastatin NLC dispersions into a gel form and assessed their potential for anti-inflammatory activity. We used two solid lipids, Compritol 888 ATO and GMS, along with oleic acid as a liquid lipid. The results indicated that this formulation provided sustained anti-inflammatory effects in the animals tested. The NLC gel demonstrated good stability, rheological properties and safety for topical application. Based on these findings, preparing an NLC gel appears Optimistic for the topical delivery of simvastatin. The optimized batch (F-II) had 78% EE, 148.4 nm particle sizes, 0.369 PDI, -2.90 mV ZP and 89.6% drug content. Stability studies confirmed robustness and PII was 0.11, indicating negligible irritation.

Future research could explore optimizing the gel formulation to further enhance its penetration into deeper skin layers. Clinical trials involving human subjects would be essential to confirm the efficacy and safety observed in animal models. Additionally, studying the formulation's compatibility with other therapeutic agents could expand its application scope in dermatological treatments.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The protocol of animal study was approved by IAEC of Modern College of Pharmacy, Nigdi, Pune with approval No. MCP/IAEC/21/2016.

ABBREVIATIONS

NLCs: Nanostructured lipid carriers; **HPH:** High-speed homogenization; **PII:** Primary irritation index; **DDS:** Drug delivery systems; **SLNs:** Solid lipid nanoparticles; **Simvastatin:** SMV; **EE:** Entrapment efficiency; **ZP:** Zeta potential; **PDI:** Polydispersity index; **PSD:** Particle size distribution.

SUMMARY

In this study, NLCs loaded with simvastatin were developed using Compritol 888 ATO and glyceryl monostearate as solid lipids, along with oleic acid and linseed oil as liquid lipids. Formulation II and B were selected based on high drug %EE and drug content, uniform particle size distribution and acceptable ZP and PDI. These NLCs were then incorporated into gel formulations using Carbopol 934, showing good stability, rheological properties and skin compatibility. *In vitro* drug release studies demonstrated sustained release profiles and *in vivo* anti-inflammatory evaluations in rats revealed significant reductions in paw edema, with formulations II and B achieving approximately 59.40% and 55.64% inhibition, respectively. Overall, NLC gel formulations present an optimistic approach for enhancing the topical delivery and therapeutic efficacy of simvastatin.

REFERENCES

1. Patidar A, Thakur DS, Kumar P, Verma J. A review on novel lipid based nanocarriers. Int J Pharm Pharm Sci. 2010;2(4):30-5.
2. Patel DK, Tripathy S, Nair SK, Kesharwani R. Nanostructured lipid carrier (NLC) a modern approach for topical delivery: a review. World J. Pharm. Pharm. Sci. 2013;2(3):921-38.
3. Attama AA, Momoh MA, Builders PF. Lipid nanoparticulate DDS: a revolution in dosage form design and development. Recent advances in novel drug carrier systems. 2012;5:107-40.
4. Muller RH. Arzneistofftrager aus festen lipidteilchen (Feste Lipidnanospharen (SLN)). Eur. Patent EP 0605497 B1. 1996.
5. Schwarz C, Mehnert W, Lucks JS, Müller RH. Solid lipid nanoparticles (SLN) for controlled drug delivery. I. Production, characterization and sterilization. J Control Release. 1994;30(1):83-96.
6. Muller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and Nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations, Adv Drug Deliv Rev. 2002;54(1):131-55.
7. Teeranachaideekul V, Boonme P, Souto EB, Muller RH, Junyaprasert VB. Influence of oil content on physicochemical properties and skin distribution of Nile red-loaded NLC, J Control Release. 2008;128(2):134-41.
8. Souto EB, Wissing SA, Barbosa CM, Muller RH. Development of a controlled release formulation based on SLN and NLC for topical clotrimazole delivery, Int J Pharm. 2004;278:71-7.
9. Muller RH, Petersen RD, Hommoss A, Pardeike J. Nanostructured lipid carrier (NLC) in cosmetic dermal products. Adv Drug Deliv Rev. 2007;59:522-30.
10. Schafer-Korting M, Mehnert W, Korting HC. Lipid nanoparticles for improved topical application of drugs for skin diseases, Adv Drug Deliv Rev. 2007;59(6):427-30.
11. Müller R, Pardeike J. Coenzyme Q10-loaded NLCs: preparation, occlusive properties and penetration enhancement. Pharm Technol Eur. 2007;19(7).
12. Teeranachaideekul V, Muller RH, Junyaprasert VB. Encapsulation of ascorbyl palmitate in nanostructured lipid carriers (NLC)-effects of formulation parameters on physicochemical stability, Int J Pharm. 2007;340(1- 2):198-206.
13. Jenning V, Gohla SH. Encapsulation of retinoids in solid lipid nanoparticles (SLN). J Microencapsul. 2001;18(2):149-58.
14. Flynn GL. In Percutaneous absorption, Bronaugh R L, H I Maibach. Eds. Marcel Dekker Inc. New York. 1985;17-52.
15. Kasting GB, Smith RL anderson BD. In Pro-drugs: topical and ocular drug delivery, Sloan, K., Ed. Marcel Dekker Inc.: New York. 1992:117-61.
16. Kriwet K, Müller RH, Goymann CC. Diclofenac release from phospholipid drug systems and permeation through excised human stratum corneum. Int J Pharm. 1995;125:231-42.
17. Morrow DI, McCarron PA, Woolfson AD, Donnelly RF. Innovative strategies for enhancing topical and transdermal drug delivery. The Open Drug Delivery Journal. 2007; 1(1); 1: 36-59.
18. Bach M, Lippold BC. Percutaneous penetration enhancement and its quantification. Eur J Pharm Biopharm. 1998;46(1):1-3.
19. Colombo ML. An update on vitamin E, tocopherol and tocotrienol-perspectives. Molecules. 2010;15(4):2103-113.
20. Wang L, Newman RK, Newman CW, Jackson LL, Hofer PJ. Tocotrienol and fatty acid composition of barley oil and their effects on lipid metabolism. Plant Foods Hum Nutr. 1993;43:9-17.

21. Sookwong P, Nakagawa K, Murata K, Kojima Y, Miyazawa T. Quantitation of tocotrienol and tocopherol in various rice brans. J Agric Food Chem. 2007;55(2):461-6.
22. Nair HA, Soni DM. Optimization of formulation parameters for preparation of docetaxel loaded nanostructured lipid carriers. Int J Pharm Sci Res. 20151;6(7): 2846-57.
23. Garse H, Jagtap P, Dand N, Kadam V. Studies on lipid nanoparticle formulation of antihyperlipidemic drug. World J Pharm Sci. 2015:438-47.
24. Üner M, Karaman EF, Aydoğmuş Z. Solid lipid nanoparticles and nanostructured lipid carriers of loratadine for topical application: physicochemical stability and drug penetration through rat skin. Trop j pharm res. 2014;13(5):653-60.
25. Tichota DM, Silva AC, Sousa Lobo JM, Amaral MH. Design, characterization and clinical evaluation of argan oil nanostructured lipid carriers to improve skin hydration. Int J Nanomedicine. 2014:3855-64.
26. Dandagi PM, Dessai GA, Gadad AP, Desai VB. Formulation and evaluation of nanostructured lipid carrier (NLC) of lornoxicam. Int J Pharm Pharm Sci. 2014;6(2):73-7.
27. Shekhawat PB. Preparation and evaluation of clotrimazole nanostructured lipid carrier for topical delivery. Int J Pharm Bio Sci. 2013;4(1):407-16.
28. Shinde G, Rajesh KS, Prajapati N, Murthy RS. Formulation, development and characterization of nanostructured lipid carrier (NLC) loaded gel for psoriasis. Sch Res J. 2013;5(4):13-25.
29. Sanap GS, Mohanta GP. Design and evaluation of miconazole nitrate loaded nanostructured lipid carriers (NLC) for improving the antifungal therapy. J Appl Pharm Sci. 2013;3(1):46-54.
30. 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. Scientia pharmaceutica. 2012 80(3):749-64.
31. Pokharkar VB, Shekhawat PB, Dhapte VV, Mandpe LP. Development and optimization of eugenol loaded nanostructured lipid carriers for periodontal delivery. Int J Pharm Pharm Sci. 2011;3(4):138-43.
32. Sanad RA, AbdelMalak NS, Elbayoomy TS, Badawi AA. Formulation of a novel oxybenzone-loaded nanostructured lipid carriers (NLCs). Aaps Pharmscitech. 2010;11:1684-94.
33. Gokce EH, Korkmaz E, Dellera E, Sandri G, Bonferoni MC, Ozer O. Resveratrol-loaded solid lipid nanoparticles versus nanostructured lipid carriers: evaluation of antioxidant potential for dermal applications. Int J Nanomedicine. 2012:1841-50.
34. Blake GJ, Ridker PM. Are statins anti-inflammatory?. Trials. 2000;1:1-5.
35. Weitz-Schmidt G. Statins as anti-inflammatory agents. Trends Pharmacol Sci. 2002;23(10):482-6.
36. Bu DX, Griffin G, Lichtman AH. Mechanisms for the anti-inflammatory effects of statins. Curr Opin Lipidol. 2011;22(3):165-70.
37. Al-Ghoul WM, Kim MS, Fazal N, Azim AC, Ali A. Evidence for simvastatin anti-inflammatory actions based on quantitative analyses of NETosis and other inflammation/oxidation markers. Results in Immunology. 2014;4:14-22.
38. Leung BP, Sattar N, Crilly A, Prach M, McCarey DW, Payne H, Madhok R, Campbell C, Gracie JA, Liew FY, McInnes IB. A novel anti-inflammatory role for simvastatin in inflammatory arthritis. J Immunol. 2003;170(3):1524-30.
39. Venkatesh RS, Patchva LD, Muppa S. Study of anti-inflammatory effect of simvastatin in rats. Int J Basic Clin Pharmacol. 2016;5(4):1520.

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