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RESEARCH ARTICLE

FORMULATION & CHARACTERIZATION OF NANOSTRUCTURED LIPID CARRIER (NLC) BASED GEL FOR TOPICAL DELIVERY OF ETORICOXIB**Sachan Anupam Kr. *, Gupta Ankita and Arora Mona**

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ABSTRACT

Nanostructured lipid carriers (NLC)-based topical gel of Etoricoxib was prepared with the aim for the treatment of inflammation and allied conditions. The composition of NLC consisted of Stearic acid as solid lipid, oleic acid as liquid lipid and tween 80 as a surfactant. NLCs prepared by melt-emulsification and low temperature solidification techniques were characterized by particle sizing technology, scanning electron microscopy (SEM), and differential scanning calorimetry (DSC). All of the NLC showed high entrapment efficiency ranging from 69% to 76%. Both the entrapment and release rate were affected by the percentage of oleic acid. NLC-F3G-C was selected as best formulation with average particle size of 244 nm and polydispersity index of 0.690 indicating homogeneity in particle size distribution. The higher magnitude of zeta potential of NLC-F3G-C indicates the stability of formulation. The nanoparticulate dispersion was suitably gelled and assessed for Physical appearance, Homogeneity, Spreadability and *in-vitro* permeation study. *In-vitro* drug release pattern of developed NLC dispersion gel showed burst and prolong release. It was concluded that developed NLC gel of Etoricoxib holds promise for prolonged availability of drug in the skin tissues and can be used for better management of inflammatory conditions.

Keywords: Etoricoxib • Nanostructured lipid carriers (NLC) • Topical gel • Nanoparticle**INTRODUCTION**

Solid lipid nanoparticles and nanostructured lipid carriers have attracted much attention in the last decade in transdermal drug delivery. Solid lipid nanoparticles (SLNs) are identical to an oil-in-water emulsion wherein the liquid lipid (oil) of the emulsion has been replaced by a solid lipid that has a liquid- to-solid phase transition well above the body temperature (37°C).¹ SLNs are colloidal particles containing highly purified triglycerides, composed mainly of lipids that are solid at room temperature and further stabilized by surfactants.² SLNs are produced by one of the following techniques³, viz. High Pressure Homogenization, High Shear Homogenization, Microemulsion Templates, Solvent Injection Method employing water-insoluble solvent, and Solvent Emulsification Diffusion method using a partially water-miscible solvent⁴. To overcome some of the limitations of SLNs, viz. limited drug loading and drug leakage during storage, nanostructured lipid carriers (NLC) have been developed. They consist of a solid lipid matrix with a high content of liquid lipid. These carriers are composed of physiological and biodegradable lipid, exhibiting low systemic toxicity and low cytotoxicity⁵. The small size of lipid particles ensure close contact to the stratum corneum and can enhance drug flux through the skin, and due to their solid lipid

matrix, a controlled release from these carriers are possible.⁶

Etoricoxib is a nonsteroidal anti-inflammatory drug that acts by inhibition of cyclooxygenase II (COX-II) and is used in the treatment of inflammation and arthritis. An arthritic condition demands a controlled-release drug delivery system for a prolonged period to satisfy the goals of treatment like reducing pain and inflammation, slowing disease progression, and preventing adverse reactions. Therefore the aim of the study was to design Etoricoxib loaded Nanostructured lipid carrier (NLCs) gel for topical delivery that could not only increase delivery of drug locally and improve the release of the drug for a prolonged period, but also reduce the risk of gastrointestinal side effects and toxicity.

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MATERIALS AND METHODS

MATERIALS

Etoricoxib was obtained as a gift from Unison Pharmaceuticals, Baddi, India. Carbopol 940 was a kind gift sample from Guapha Pharmaceuticals, INDIA. Stearic acid, Oleic acid & Glycerol were purchased from Fizmerk India chemicals, Hapur (U.P), INDIA. All other chemicals were of analytical grade.

Solubility Study

The solubility of Etoricoxib was determined in distilled water and Phosphate buffer solutions of pH 4.0, 5.0, 6.0, 6.4, 6.8, 7.0, 7.2, 7.4, 7.6. An excess amount of drug was added to 10ml of different solvent. The contents were stirred continuously for 24 hours at 37°C and allowed to equilibrate. After 24 hours the sample were withdrawn and filtered through membrane filter and the filtrate were suitably diluted with an appropriate solvent and analyzed spectrophotometrically (UV-1371, electronic India, INDIA) for Etoricoxib concentrations, at 233 nm with reference to a corresponding calibration curve. Each experiment was done in triplicate and the equilibrium solubility was recorded.^{7,8}

Partition Coefficient Study

Equal volumes of distilled water, buffer solutions of pH 4.0, 5.0, 6.0, 6.4, 6.8, 7.2, 7.4, 7.6 and isopropyl myristate (IPM) were previously saturated with each

other by shaking together in shaker for 3 hours and the two phases were left to separate overnight. To each of the separated IPM phases, a known concentration of Etoricoxib was added with gentle shaking until dissolved. The mixtures were then agitated for 6 hours at room temperature, and the two phases were left to separate again. The drug concentration in aqueous phases was determined spectrophotometrically at 233 nm, after suitable dilution. The results, treated according to Equation.⁹

$$\text{Partition Coefficient} = \frac{\text{Concentration in Organic Phase}}{\text{Concentration in Aqueous Phase}}$$

Preparation of NLC Dispersion

Melt emulsification and low-temperature Solidification method: Etoricoxib was dissolved in methanol and mixed with acetone solution containing blend of stearic acid and oleic acid (SA+OA). The mixture was sonicated for 15 minute, and then added drop wise to tween 80 solutions, stirred at 3000 rpm using magnetic stirrer (Remi instruments Ltd., Mumbai, India) for 30 min at 70°C temperature. The mixed solution was transferred to icy water bath and stirred for four hour at 3000 rpm. The NLC dispersions were lyophilized for further study.¹⁰ The formulations variables are tabulated in table 1.

Table 1: Composition of different NLC dispersion (batch size 100g)

Formulation Code	Lipid		Tween 80	Drug	Water	Final Amount
	Stearic acid	Oleic acid				
BLANK	0.9g	0.1g	2.5g	NIL	96.4g	100g
NLC-F1	0.9g	0.1g	2.5g	0.1g	96.5g	100g
NLC-F2	0.8g	0.2g	2.5g	0.1g	96.4g	100g
NLC-F3	0.7g	0.3g	2.5g	0.1g	96.4g	100g

Characterization of NLC Dispersion

Particle size and Polydispersity Index Distribution

Particle size and polydispersity index (PI) which is a measure of the distribution of nanoparticle population were determined by using Malvern Mastersizer 2000MU (Malvern instrument UK detection limit 0.01–1,000 μm). The obtained data were evaluated using the volume distribution (d_{10%}, d_{50%}, d_{90%}) which means that if the diameter 90% (d_{90%}) is registered as 1 μm, this indicates that 90% of particles have a diameter of 1 μm or lower. The PI was measured by the span which can be calculated from the following equation.

Where d_{90%} is the particle diameter at 90% cumulative size, d_{10%} is the particle diameter at 10% cumulative size, and d_{50%} is the particle diameter at 50% cumulative size.¹¹

$$\text{SPAN} = \frac{D_{90\%} - D_{10\%}}{D_{50\%}}$$

Zeta Potential (ζ)

The zeta potential was measured by using the Zetasizer 2000 (Malvern Instruments, UK). Zeta potential is the electric potential of a particle in a suspension. It is a parameter which is very useful for the assessment of the physical stability of colloidal dispersions. In suspensions the surfaces of particles develop a charge due to ionization of surface groups or adsorption of ions. This charge depends on both the surface chemistry of the particles and the media around these particles.

Scanning Electron Microscopy

The morphological characteristics of NLC was studied by scanning electron microscope (JEOL-JSM-6360 JAPAN). One drop of sample was placed on a slide and excess water was left to dry at room temperature. Further the slide was attached to the specimen holder using a double coated adhesive tape and gold coated under vacuum using a sputter coater (Model JFC-1100, Jeol, JAPAN) for 10 minute and investigated at 20kV.¹²

Drug entrapment efficiency and drug loading determination

A volume of 2.0 ml of each drug-loaded sample was centrifuged at 12500 rpm for 45 min to separate the lipid and aqueous phase. The supernatant was then diluted with methanol and analyzed by UV-VIS spectrophotometer (UV-1800 Shimadzu spectrophotometer) at 233 nm. The entrapment efficacy of nanoparticles was calculated as follows:

$$EE = \frac{(W_a - W_s)}{W_a} \times 100$$

$$DL = \left(\frac{W_a - W_s}{W_a - W_s + W_l} \right) \times 100$$

Where EE is entrapment efficiency, DL is Drug loading, W_a stands for the mass of Etoricoxib added to the formulation and W_s is the analyzed weight of drug in supernatant and W_l is weight of lipid added.^{13, 14, 15}

Infra-red spectroscopy

An IR spectrum reveals the characteristic peaks of all functional groups present in a sample. In order to ascertain successful entrapment, the drug, lipid, their physical mixture and NLC were subjected to FTIR studies. IR spectra of Etoricoxib (ETORI), stearic acid (SA), physical mixture of stearic acid and oleic acid (SA+OA), blank NLC and etoricoxib loaded NLC formulation were recorded using IR Spectrophotometer (Shimadzu model 8400) between the range of 500 cm^{-1} to 4000 cm^{-1} .

Thermal analysis

Differential Scanning Calorimeter Analysis (DSC)

DSC analysis of Etoricoxib (ETORI), stearic acid (SA), physical mixture of stearic acid and oleic acid (SA+OA), and NLC formulation were performed using Perkin-Elmer DSC model. The instrument was calibrated with indium. All the samples (5mg) were heated in aluminum pans using dry nitrogen as the effluent gas. The analysis was performed with a heating range of 20-240 $^{\circ}\text{C}$ and at a rate of 10 $^{\circ}\text{C}/\text{minute}$.¹⁶

Stability studies

The chemical and physical stabilities of NLC dispersions were evaluated at 2-8 $^{\circ}\text{C}$ for 1 month for its clarity, particle size, and drug content.

PREPARATION OF ETORICOXIB LOADED NLC GEL^{17, 18}

Based on the previously mentioned characterizations (particle size, entrapment efficiency and in vitro release profile of NLC dispersion) NLC formulation with optimum physicochemical properties were selected. NLC gel was prepared by dispersing carbopol 940 in small quantity of distilled water to prepare aqueous dispersion, which was then allowed to hydrate for 4 to 5 hour. Glycerol (10% w/w) was added subsequently to the aqueous dispersion and the Lyophilized NLC powder equivalent to 1.0% of Etoricoxib was incorporated in it. Triethanolamine was added to the above dispersion using an overhead stirrer at speed of 1200 rpm (Remi Motor, India). Stirring was continued till the carbopol got dispersed. The gel was allowed to stand overnight to remove entrapped air. The NLC gel was also prepared by using HPMC by above method. Composition of NLC Gel formulation shown in Table 2.

2: Composition of NLC Gel formulation

Composition (% w/w)	Formulation Code	
	NLC-F1G-C	NLC-F1G-HPMC
Carbopol 940P	1%	1%
Lyophilized NLC (NLC eq to 1.0%)	1.0%	1.0%
Glycerin	10%	10%
Triethanolamine	q.s.	q.s.
Distilled water	q.s.	q.s.

EVALUATION OF NLC GEL

Physical appearance & Homogeneity

Physical appearance and homogeneity of gel was observed visually.

Spreadability study of NLC gel

The spreadability of the gel formulations was determined at 24h after preparation, by measuring the spreading diameter of 1gm gel between two horizontal plates (20 x 20 cm^2) after 1 minute. The standardized weight tied on the upper plate was 220gm. The spreadability was calculated by using the following formula.

$$S = M \times L/T$$

Where S is spreadability, M is weight tied on upper slide. L is the length of glass slide, t is time taken.¹⁹

In-vitro drug release studies of NLC based gel

The in vitro release studies were performed using modified Franz diffusion cell to evaluate the amount of Etoricoxib released from each formulation. Dialysis membrane 70 (Hi-Media, Mumbai, India) having pore size 2.4 nm and surface area of 3.14 cm^2 . The receptor medium was approximately 45 ml and composed of phosphate buffer saline (PBS), pH 7.4, and stirred by magnetic bar at 700 rpm to avoid different concentrations within the acceptor medium and to minimize stagnant layers. NLC dispersion (equivalent to 1mg of drug) was placed in the donor compartment. During the experiments, the solution in receptor side

was maintained at $37^{\circ}\text{C}\pm 0.5^{\circ}\text{C}$. After certain time interval, 3ml of the sample medium was withdrawn from receiver compartment through side tube and same volumes of freshly prepared receptor medium were added. The samples were analyzed by UV-Visible spectrophotometer at 233nm. For each formulation, the release studies were performed in triplicate.

Permeation data analysis

The permeation profiles were constructed by plotting the cumulative amount of Etoricoxib permeated per unit dialysis membrane area ($\mu\text{g}/\text{cm}^2$) versus time. The steady state flux (J_{ss} , $\mu\text{g}/\text{cm}^2/\text{hr}$) of Etoricoxib was calculated from the slope of the plot using linear regression analysis. The permeability co-efficient (K_p) of the drug through the membrane was calculated using the following equation.

$$K_p = \frac{J_{ss}}{C}$$

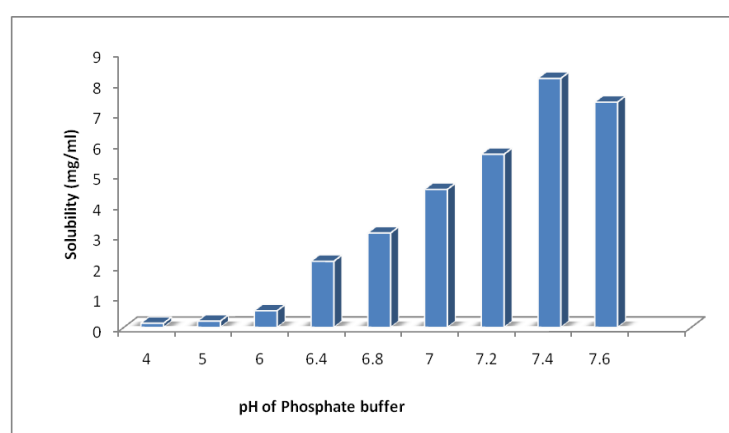


Figure 1: Solubility Profile of Etoricoxib in different phosphate buffer

Apparent partition coefficient of Etoricoxib

Determination of partition coefficient of drug is essential as it affects entrapment efficiency as well as release of drug from the formulation. Isopropyl myristate (IPM) was chosen as lipophilic phase in partitioning experiment, because its polar and non-polar properties can simulate skin lipids.²¹ The apparent partition coefficient values in Table 3, indicated an expected increase in the lipophilicity of the acidic drug, like Etoricoxib, by decreasing the pH value. While at pH 7.4, the drug was completely ionized, so the partition coefficient decreased. From this study, it was shown that Etoricoxib had moderate lipid and aqueous solubility. Hence, the drug could be considered as a good candidate for transdermal drug delivery system, as it can be soluble in the sebum of the skin, and then readily penetrate into the lower skin layers to dissolve in the tissue fluids.

Preparation and Characterization of NLC Dispersion

The Etoricoxib loaded NLC containing different blends of stearic acid and oleic acid (SA+OA) were prepared by melt emulsification and low-temperature solidification method. In particle sizing technology, span is a measure

Where, C is the initial concentration of the drug in the donor compartment. The penetration enhancing effect was calculated in terms of enhancement ratio (Er) by using the following equation.²⁰

$$Er = \frac{J_{ss} \text{ of formulation}}{J_{ss} \text{ of control}}$$

RESULT AND DISCUSSION

Solubility profile of Etoricoxib

The solubility profile of Etoricoxib in phosphate buffer of different pH was determined. It can be seen from the Figure 1 that solubility of the drug increased with increase in pH up to pH 7.4, and then the solubility decreased. The solubility of Etoricoxib in phosphate buffers of pH 6.8 and 7.4 at $37^{\circ}\text{C}\pm 0.5^{\circ}\text{C}$ after 24h were 3.088 mg/ml and 8.151 mg/ml respectively.

of the poly-dispersity index (PI) i.e. particle homogeneity and it varies from 0 to 1.

Table 3: Apparent Partition coefficient of Etoricoxib in PBS

System	Apparent Partition coefficient*
IPM / pH 4 Buffer	22.705 ± 1.20
IPM / pH 5 Buffer	15.00 ± 0.870
IPM / pH 6 Buffer	9.35 ± 1.22
IPM / pH 6.4 Buffer	8.188 ± 0.33
IPM / pH 6.8 Buffer	5.449 ± 0.52
IPM / pH 7.0 Buffer	2.598 ± 0.538
IPM / pH 7.2 Buffer	3.055 ± 0.087
IPM / pH 7.4 Buffer	2.379 ± 0.557
IPM / pH 7.6 Buffer	4.206 ± 0.532
IPM / Water	24.579 ± 1.46

*Mean ± S.D

The d_{90} for nanoparticulate dispersion determined using Malvern Mastersizer showed size ranging from 244 to 2831 nanometer. NLC-F3 had polydispersity index of 0.690 indicated homogeneity in particle size distribution (Figure 2). The drug entrapment efficiency and drug

loading capacity of NLC-F1 & F3 were increased from 69% to 76% and from 6.45 to 7.06% respectively, on increasing the percentage of OA from 10 to 30 wt%. It might be due to the incorporation of liquid lipids to solid lipids which could lead to massive crystal order disturbance, and the resulting matrix of lipid particles had great imperfections in the crystal lattice and leaves enough space to accommodate drug molecules, thus,

leading to improved drug loading capacity and drug entrapment efficiency. Higher entrapment in formulation containing 30% oleic acid also indicates the higher solubility of Etoricoxib in oleic acid as compare to stearic acid. The particle size distribution, span values, %Entrapment efficiency, %Drug loading of NLC are presented in Table 4.

Table 4: Particle size distribution of different formulations of NLC and Blank formulation

Formulation code	Mean volume distribution			Span	Percentage Entrapment efficiency*	Percentage Drug loading*
	d ₁₀ %	d ₅₀ %	d ₉₀ %			
NLC-F1	0.129	0.183	11.094	59.91	69.33 ± 0.57	6.48 ± 0.05
NLC-F2	0.145	0.537	23.528	43.54	72.00 ± 2.00	6.71 ± 0.175
NLC-F3	0.126	0.171	0.244	0.690	76.33 ± 1.527	7.08 ± 0.132
B-NLC(Blank)	0.492	0.789	2.831	2.964	-	-

*Mean ± S.D

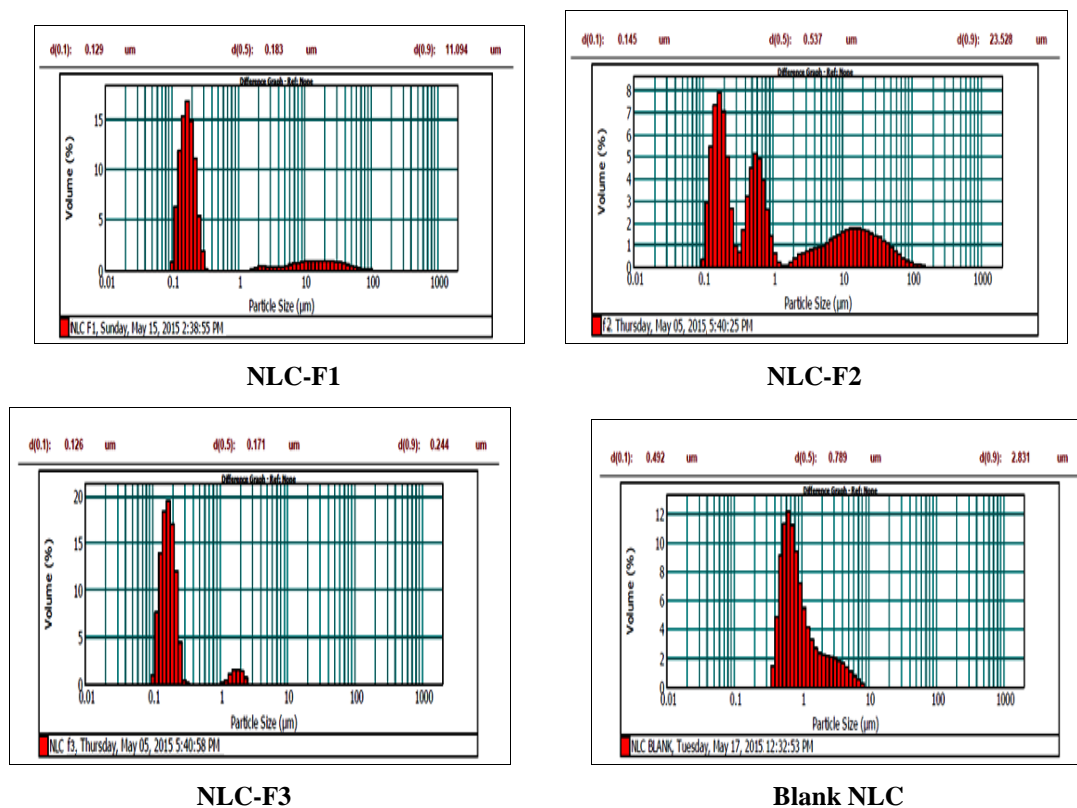


Figure 2: Particle size distribution graphs of different formulations of NLC and Blank formulation

Zeta Potential (ζ)

The zeta potential graph of the NLC dispersion is given in Figure 3. The surface charge values are negative for empty and drug-loaded samples. Moreover, these values are lower in drug-loaded samples than empty e.g. zeta potential of blank NLC was -12.7 while for NLC-F1, NLC-F2 and NLC-F3 dispersion it was -11.2, -11.9 and -11.8. The presence of drug causes a diminution of surface charge of all the investigated samples. Moreover samples have different zeta potential values because the surface charge depends on lipid matrix used. The higher

magnitude of zeta potential indicates the stability of formulation.

Scanning Electron Microscopy

The micrograph of the NLC-F3 illustrated spherical droplets in the nanometer range (Fig. 4). The results indicated that the particles were spherical and no drug crystal of particles visible in the figure. The picture shows agglomeration of particles due to the lipid nature of the carriers. Some particle shapes deviates from spherical shape due to the lipid modification during the drying process of sample treatment.

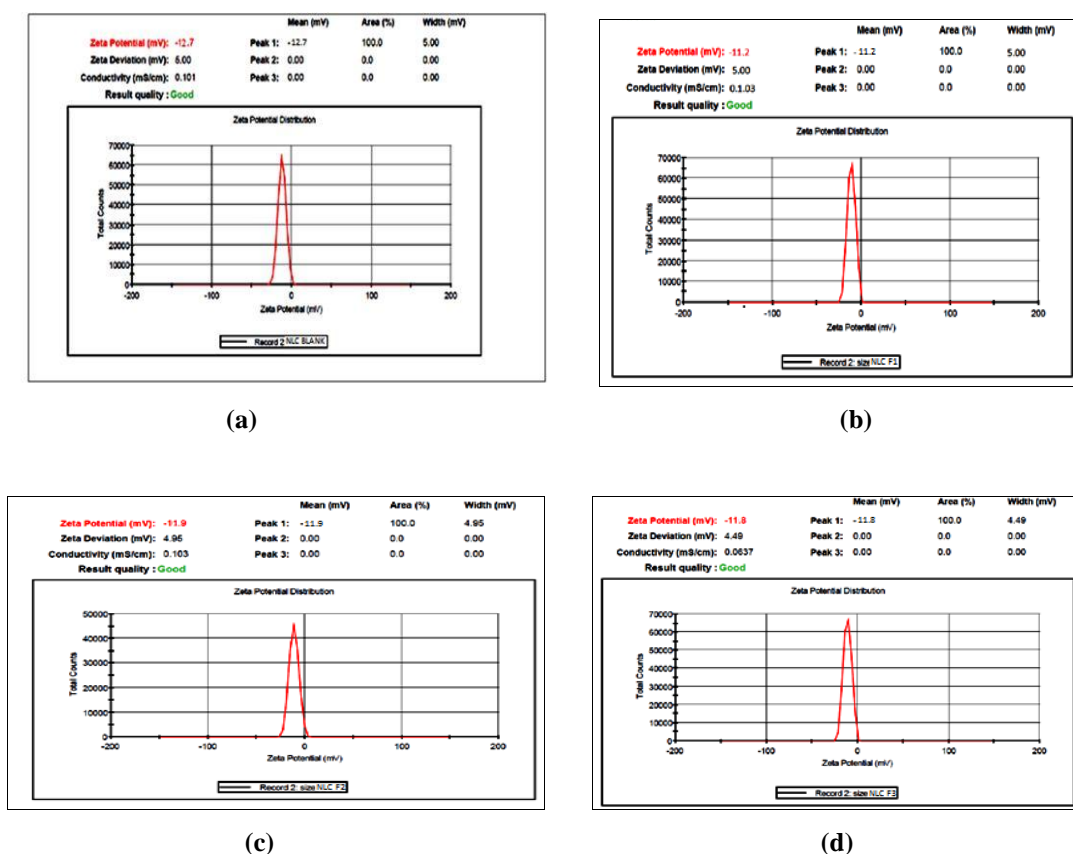


Figure 3: Zeta potential of (a) Blank NLC, (b) NLC-F1, (c) NLC-F2 and (d) NLC-F3 Dispersion respectively.

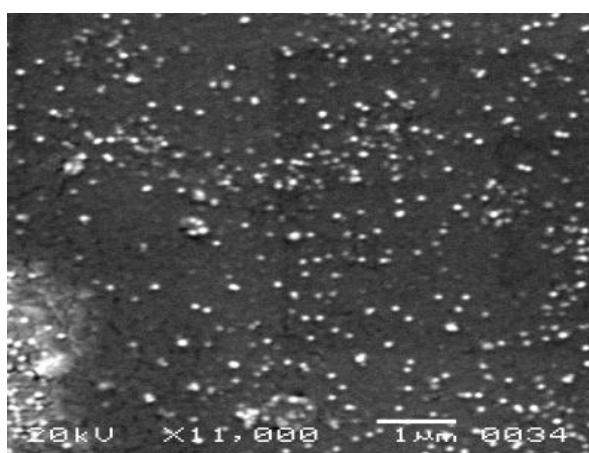


Figure 4: SEM of NLC-F3 Dispersion

Infra-red spectroscopy

For FTIR study about 1-2 mg of sample were mixed with anhydrous potassium bromide. The IR spectra of pure drug Etoricoxib, SA, SA+OA, SA+OA+ETORI, BLANK NLC, DNLC are shown in Figure 5. The IR spectrum of pure drug, Etoricoxib, which is 5-Chloro-6'-methyl-3-[4-(methylsulfonyl) phenyl]-2, 3'-bipyridine shows a peaks at 1592.9 cm^{-1} (C=N stretching vibration), 1430.0, 1299.4, 1136.8, and 1089.6 cm^{-1} (S=O stretching vibration) and 834.0, 777.1, and 639.22009 cm^{-1} (C-Cl stretching vibration). However, in the IR spectrum of Etoricoxib loaded NLC (Figure 5f) peaks of CN group and C-Cl group are absent. It is evident that the IR spectrum of NLC resembles that of

the lipid thus proving that the lipid forms the outer core and the drug has been successfully incorporated inside it²².

Thermal analysis

Differential Scanning Calorimeter Analysis (DSC)

Differential scanning calorimetry enables the quantitative detection of all processes in which energy is required or produced (i.e., endothermic and exothermic phase transformations).²³ It is considered as a tool to investigate the melting behavior of crystalline materials like solid lipid nanoparticles. Main purpose of this test was to inspect whether or not the crystallinity was different in the lipid nanoparticles compared with the raw materials. Blended matrix of lipid shows a melting point depression as compared to solid lipid. E.g. melting point of stearic acid was 67.81⁰C but mixture of stearic acid (70%) and oleic acid (30%) showed a melting point depression 58.17⁰ C. DSC thermogram of Etoricoxib showed endothermic peak at 136.12⁰C as evident in Figure 6 (a), which is the reported melting point of the drug.²⁴ Drug loaded NLC in Figure 6 (d), showed a large endothermic peak at 58.93⁰C and disappearance of the drug peak suggesting a molecular dispersion of Etoricoxib into the loaded NLC and that Etoricoxib exists in amorphous state rather than in crystalline state. Furthermore, the inclusion of drug molecules in the lipid is normally accompanied by a depression in the lipid's melting point.^{25, 26}

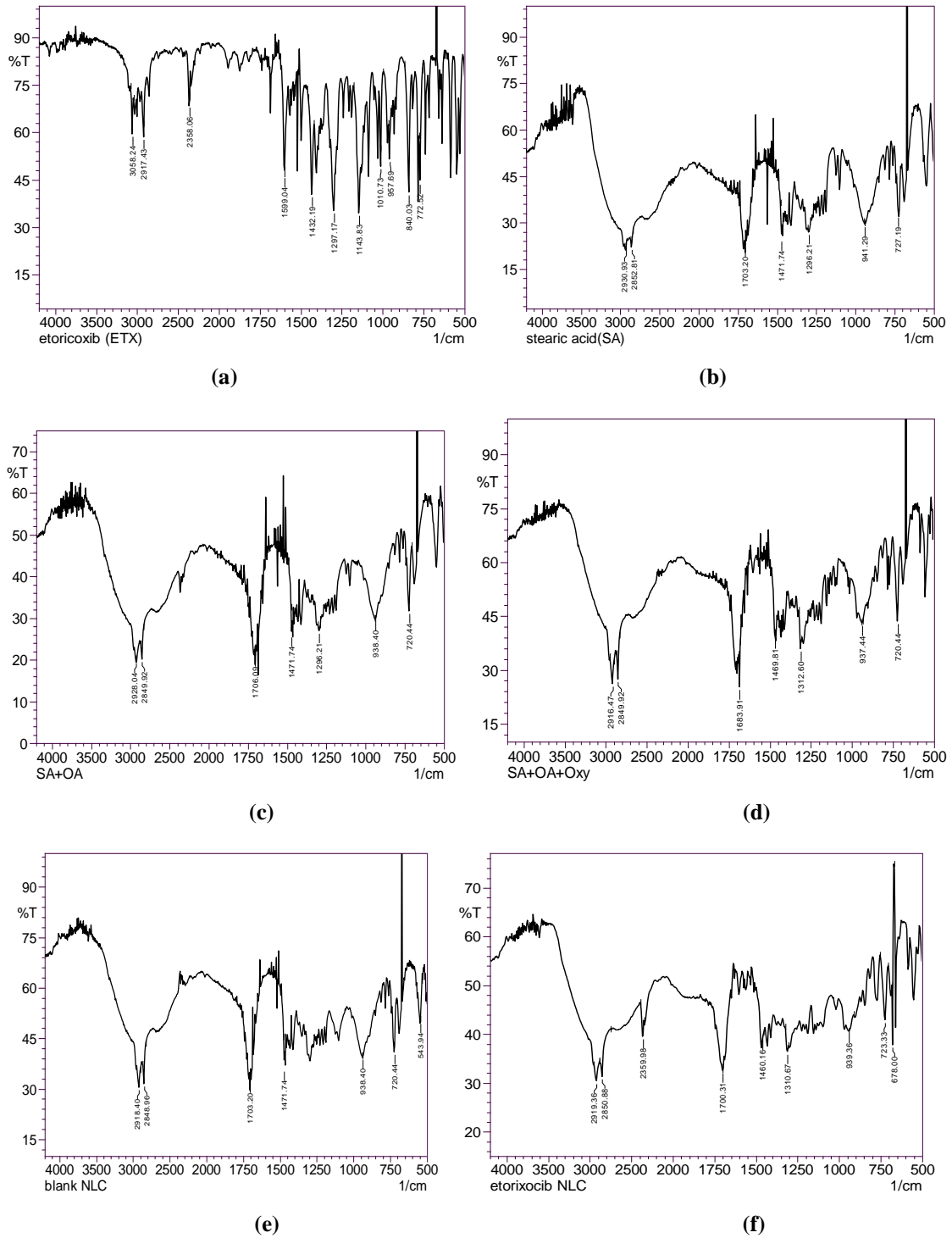


Figure 5: IR spectrum of (a) Etoricoxib, (b) Stearic acid, (c) Stearic acid + oleic acid, (d) Stearic acid + oleic acid + Etoricoxib, (e) BLANK NLC and (f) Etoricoxib loaded NLC respectively.

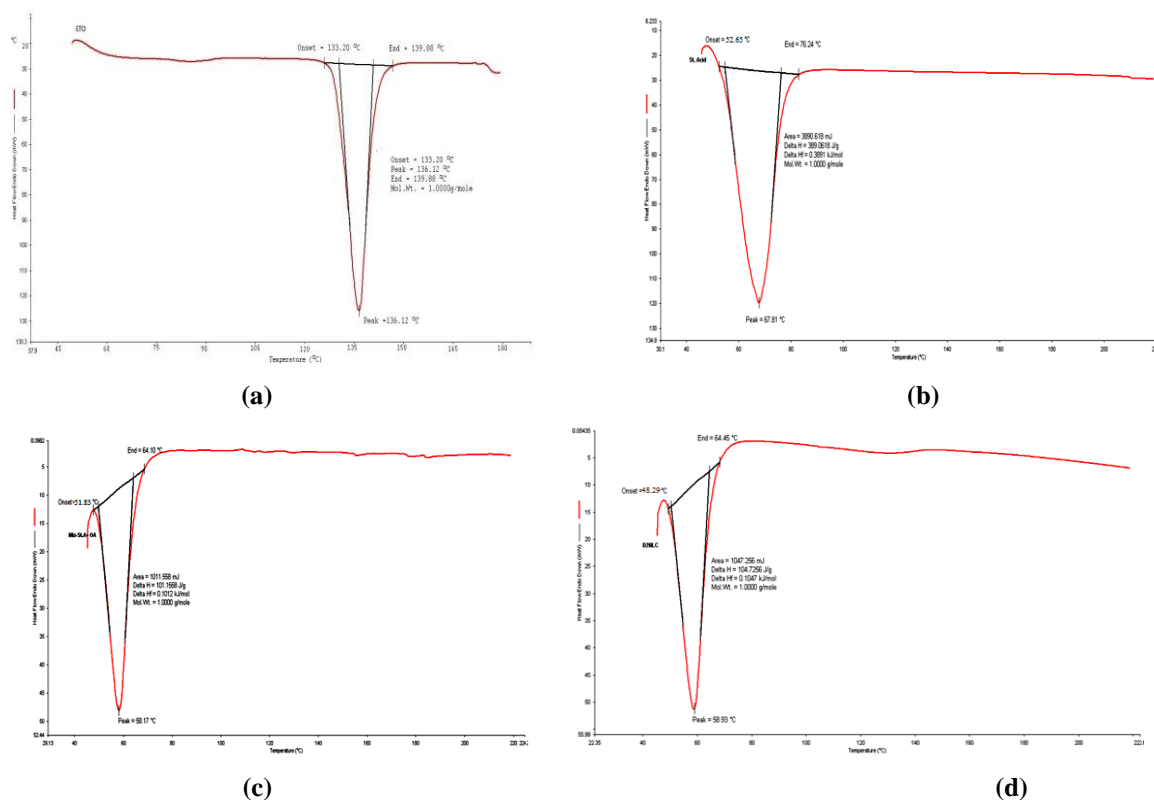


Figure 6: DSC graph of (a) Etoricoxib, (b) Stearic acid, (c) Stearic acid + oleic acid, (d) Etoricoxib loaded NLC respectively.

Stability study

After one month refrigerated storage the NLC dispersion showed little difference in particle size and entrapment efficiency. No obvious change in clarity and degradation was observed.

Centrifugation at 3000 rpm for 30 min also showed that the NLC dispersions had a good physical stability

Preparation and Evaluation of Etoricoxib Loaded NLC Gel

Based on the particle size, entrapment efficiency NLC-F3 formulation having optimum physicochemical properties were selected for preparation of topical gel. Lyophilized NLC powder was incorporated into the gel. The physical appearance of drug loaded NLC gel was

found to be off-white in color, smooth in texture and translucent. All the formulation was found to be homogenous. Formulated gel was also evaluated for spreadability study (Table 5).²⁷ Spreadability means the area to which the gel rapidly spread on application to skin or affected part of skin. The obtained value indicated a good spreadability of formulated gel preparations. Spreadability is an essential property for topical preparations. A gel application on the inflamed skin or diseased skin would be more comfortable if it can be spread easily. In general, the gels that possess a low consistency index are more spreadable. The release of the drug from the formulation is governed by its components as well as by the consistency of the formulation.

Table 5: Spreadability data of NLC-F3G-C and NLC-F3G-HPMC gels (*Mean ± S.D.)

Formulation Code	Spreadability* (g.cm/sec)
NLC-F3G-C	200.174 ± 5.498
NLC-F3G- HPMC	206.72± 4.466

In vitro release study of NLC gel

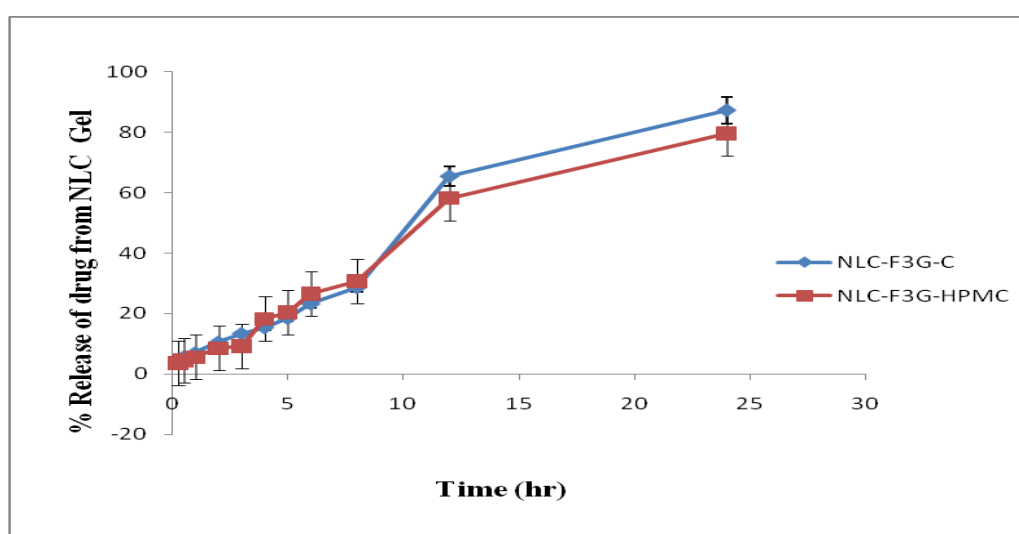
In vitro studies were performed to determine the release rate of the drug from the NLC gel formulations. The cumulative percentage release of Etoricoxib from NLC gel was investigated for a period of 24 hours (Table 6). Each sample was analyzed in triplicate. An initial rapid

drug release was noted in the NLC gel formulation, which could result from the time taken by the drug to diffuse across the gel. The direct exposure of NLC gel to diffusion media and quick release of drug may account for initial release in NLC gel. Figure 7 depicts the drug release profile of NLC-F3G-C and NLC-F3G-HPMC gels.

Table 6: Drug release profile of NLC-F3G-C and NLC-F3G-HPMC gels

S. No.	Time (hr)	% Release of drug from NLC gel *	
		NLC-F3G-C	NLC-F3G-HPMC
1	0.25	4.638±0.750	3.567±0.650
2	0.50	5.495±1.586	4.596±1.686
3	1.00	6.906±2.069	5.566±2.168
4	2.00	10.421±2.245	8.481±2.234
5	3.00	13.272±5.634	9.162±5.830
6	4.00	15.296±5.176	18.229±5.287
7	5.0	18.377±6.128	20.382±6.245
8	6.0	23.120±5.837	26.586±5.837
9	8.00	28.508±1.602	30.654±2.136
10	12.0	65.346±1.944	58.154±1.879
11	24.0	87.208±3.735	79.548±3.456

*Mean ± S.D.

**Figure 7: Drug release profile of NLC-F3G-C and NLC-F3G-HPMC gels**

Permeation data analysis

In vitro permeation studies were performed to compare the permeation of etoricoxib to the various NLC gel formulations i.e. NLC-F3G-C (Carbopol) and NLC-F3G-HPMC. The permeation study revealed that the permeability parameters like steady-state flux (J_{ss}), permeability coefficient (K_p), were higher in both formulations. The steady-state flux (J_{ss}) for NLC-F3G-C and NLC-F3G-HPMC were 115.445 ± 0.106 and $104.830 \pm 0.101 \mu\text{g}/\text{cm}^2/\text{hr}$ respectively.

Release order kinetics study

The release data were fitted to various kinetic models in order to calculate the release constant and regression coefficients. The kinetic models used were zero order equation, first order equation, Higuchi model and Korsmeyer-Peppas model. The regression coefficients for NLC-F3G-C were 0.920, 0.823, 0.888, and 0.922 and for NLC-F3G-HPMC was 0.931, 0.761, 0.937, and 0.936 respectively. The release of drugs from NLC is found to be Anomalous (non-Fickian) diffusion controlled release. NLC-F3G-HPMC exhibit Anomalous

(non-Fickian) diffusion, and closely follows Higuchi Model and also highly correlated with Korsmeyer-Peppas model and NLC-F3G-C closely follows Korsmeyer-Peppas model and also highly correlated with Higuchi Model.

CONCLUSION

Nanostructured lipid Carriers were prepared using Melt emulsification and low-temperature solidification method. FTIR and DSC studies of Etoricoxib, stearic acid, oleic acid and their physical mixture confirmed that there was no significant interaction between them. Absence of melting peak of drug in DSC of formulated NLC confirms the change in state of drug from crystalline to amorphous form. The Zeta Potential value predicted good particle stability because the repulsive forces prevent aggregation with aging. *In-vitro* drug release pattern of NLC dispersion gel showed burst and control release. Burst release as well as sustained release both are of interest for dermal application. Burst release can be useful to improve the penetration of drug while sustained release supplied the drug over a prolonged period of time.

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