

## FORMULATION AND EVALUATION OF NANOSTRUCTURED LIPID CARRIER (NLC) OF LORNOXICAM

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### ABSTRACT

**Objective:** Lornoxicam (chlortenoxicam) is a strong analgesic and anti-inflammatory NSAID of the oxycam class with better tolerability profile. It has been shown to be effective in the management of post-operative pain and rheumatoid arthritis (RA). Lornoxicam loaded nanostructured lipid carrier was prepared with the aim of minimizing the side effects of oral lornoxicam and to improve patient compliance which can give better therapeutic effects.

**Methods:** Nanostructured lipid carrier was prepared by hot homogenization method using Compritol ATO 888 (medium chain triglyceride) and Polaxomer. Drug to polymer ratio was chosen at eight levels.

**Results:** Characterization of nanostructured lipid carrier was performed by measuring particle size, zeta potential, drug entrapment efficiency and *in vitro* drug release. Spherical uniform particles (size below 500 nm) with polydispersity in the index range of 0.134 to 1.02 and negative zeta potential -25.2 mV were obtained. Drug entrapment efficiency was found to be in the range of about 79.5 % to 89.06 %. Cumulative percent drug release for all formulations after 24hrs was found to be 54.04% to 90.67%. Formulation LF5 containing 1% lipid was found to be the best formulation. Carbopol gel was prepared from optimized NLC formulation and was characterized for appearance, pH, viscosity and *in vitro* release studies. Carrageenan induced paw edema anti inflammation activity was performed and after 6 hours the % swelling inhibition was found to be 48.77%.

**Conclusion:** The results indicate that Lornoxicam loaded nanostructured lipid carrier could be utilized as a potential drug delivery system for topical applications.

**Keywords:** Lornoxicam, Compritol ATO 888, Medium Chain Triglycerides, Hot homogenization method, *In vitro* release studies, *In vivo* activity.

### INTRODUCTION

Solid lipid nanoparticle (SLN) and nanostructured lipid carrier (NLC) are colloidal lipid systems, which have been proposed for several administration routes, such as parenteral, oral and topical route providing controlled release profile of many substances. Solid lipid nanoparticle (SLN) has the chance to be exploited as a delivery system in commercial products.

However, there are some limitations of the solid lipid nanoparticles (SLN) system: Drug expulsion phenomenon when lipid crystallizes to the stable  $\beta$ -form, particle concentration in the aqueous dispersions ranging from about 1% to a maximum of only 30% and limitation of drug load by the solubility of the drug in the solid lipid.[1,2]

These limitations were solved by creating a lipid particle with a controlled nanostructure i.e the nanostructured lipid carrier (NLC). NLCs possess lower melting point due to their oil content, while maintaining their particulate character and being solid at body temperature, greater degree of drug loading, reduced burst release of drug and better control of drug release. [3]

SLN consists of pure solid lipids and NLC contains a certain percentage of additional liquid lipids leading to imperfections in the crystal lattice. These nanoparticles are produced by one of the following techniques, namely, high pressure homogenization, microemulsion template, cold homogenization, solvent emulsification, solvent diffusion, reverse micelle-double emulsion, homogenization followed by ultrasonication, solvent injection and a very recently introduced membrane contractor techniques.[4]

Lornoxicam (LOR) is a newer and highly potent NSAID that inhibits the prostaglandin synthesis and acts as a useful agent to control inflammatory conditions. Lornoxicam is especially preferred NSAID with low solubility in water and gastric fluid. The drug is characterized by a short half-life ranging from 3–5hrs. [5, 6, 7, 8]

The objective of the present study was to adopt a simple approach for the Lornoxicam NLC. Eight formulations with variable lipid concentrations were studied to optimize the formulation for maximum entrapment efficiency (EE). In addition to EE, the particle size and drug release were also considered. The other characterization studies such as zeta potential, FTIR, DSC were carried out to determine the lipid nature and size of the prepared formulations.

### MATERIALS AND METHODS

#### Materials

Lornoxicam was obtained from ZydusCadila, Himichal Pradesh, India., Compritol ATO 888 and Medium chain triglycerides from Gattefosse, France, Polaxomer from Cipla Ltd Goa, India.

#### Method for preparation of NLC

#### Preparation of LOR loaded NLCs [9, 2]

Different compositions of Lornoxicam nanostructured lipid carrier dispersions were prepared by hot homogenization technique (Table 1). In hot homogenization technique, lipids were melted at temperature ten degrees above its melting point, then Lornoxicam was added to the melted lipid. The lipid and aqueous phases were prepared separately.

The dispersion was kept at the same temperature until it appeared optically clear. Polaxomer 188 was dissolved in distilled water and heated to the same temperature of lipid mixture. Hot surfactant solution was added to the lipid phase and mixed using a high-shear homogenizer at 2000 rpm for 1 hr. The volume was made to 100 ml. The formulation was then removed from water bath and the dispersion of NLC was mixed gently at room temperature until cooled. The dispersion was further characterized for particle size analysis and entrapment efficiency.

Table 1: Composition of SLN formulation

Formulation	Drug (LOR) (mg)	Solid Lipid Compritol ATO 888 (% w/v)	Liquid Lipid Medium chain triglycerides (% w/v)	Polaxomer 188 (% w/v)	Water
LF1	16	0.2	0.2	1	q.s.
LF2	16	0.25	0.25	1	q.s.
LF3	16	0.4	0.4	1	q.s.
LF4	16	0.45	0.45	1	q.s.
LF5	16	0.5	0.5	1	q.s.
LF6	16	0.75	0.75	1	q.s.
LF7	16	1	1	1	q.s.
LF8	16	1.25	1.25	1	q.s.

### Characterization of prepared NLCs

#### FT-IR Spectroscopy [10]

FT-IR helps to confirm the identity of the drug and to detect the interaction of the drug with carriers. FT-IR spectral measurement for pure Lornoxicam drug, lipid Compritol ATO 888, and physical mixtures of Lornoxicam and Compritol ATO 888 (Fig. 1, 2, 3) were taken at ambient temperature. All the spectra acquired were scanned between 400 and 4000  $\text{cm}^{-1}$  at a resolution of 4  $\text{cm}^{-1}$ . (IRAffinity1, Shimadzu (S.No.A21374801815), Japan.)

#### DSC Analysis [10, 11]

Differential scanning calorimetry (DSC) analysis was performed on a DSC60 detector (Shimadzu Co., Japan). Approximately 5 mg of sample was weighed into an aluminium pan and sealed hermetically. DSC scan was recorded from 30 to 300  $^{\circ}\text{C}$  at a heating rate of 10  $^{\circ}\text{C}/\text{min}$  under a nitrogen purge, using an empty pan as reference. The DSC measurements were carried out for pure drug Lornoxicam and mixture of Lornoxicam and Compritol ATO 888. (Model DSC-60)

#### Particle size analysis [12, 13]

The size distribution along the volume mean diameter of the nanoparticle was measured by Dynamic Light Scattering particle size analyzer (Nanotracs particle size analyzer). The range of the analyzer is 0.02 nm to 2.8  $\mu\text{m}$ . (Microtracs Nanotracs A150, Korea.)

#### Polydispersity index [12, 13]

The polydispersity index (PDI) measured from Dynamic Light Scattering Instrument. PDI is an index of width or spread or variation within the particle size distribution. PDI can be calculated by the following equation.

$$\frac{[D_{90}-D_{10}]}{D_{50}}$$

Polydispersity =

Where  $D_{0.9}$ ,  $D_{0.1}$  and  $D_{0.5}$  particle diameter determined at 90th, 50th and 10th percentile of undesired particles respectively.

#### Zeta potential [14]

Zeta potential was measured by using Zetatrac. It is easily measured because charge of a potential will move as the suspension is placed between the two electrodes that have D.C. voltage across them and the velocity will be proportional to the zeta potential of the particle. The technical term for this is electrophoresis. (Zetatrac, Korea.)

#### Entrapment efficiency [15, 16, 4]

From the prepared NLC formulation 1ml of the dispersion was dissolved in the (1:1) mixture of 10 ml of 7.4 PBS buffer and ethanol. The mixture was centrifuged at 15,000 rpm for 40 min at 25 $^{\circ}\text{C}$  to separate free drug in the supernatant. Concentration of Lornoxicam in the supernatant was determined by UV-visible spectrophotometer at 376 nm after suitable dilution.

Entrapment efficiency was calculated using following equation. (Sigma 3K 30 Sartorius, Refrigerated Centrifuge.) (ShimadzuUV-1700 Pharmaspec (S.No. A11024504164), Japan.)

$$\frac{\text{Amount of drug actually present} \times 100}{\text{Theoretical drug load expected}}$$

Drug content =

#### In vitro drug release [17, 18]

*In vitro* release studies were performed using dialysis membrane (Hi-media, Mumbai, India) with molecular weight cut off between 12,000–14,000 Dalton. Membrane was activated with 1% of HCl solution for 12 hrs. The dissolution medium used was freshly prepared 7.4 phosphate buffer. Dialysis membrane, previously soaked overnight, was tied to one end of a specially designed glass cylinder (open at both ends). 5 ml of formulation was accurately placed into this assembly.

The cylinder was attached to a stand and suspended in 100 ml of dissolution medium maintained at 37  $\pm$  5 $^{\circ}\text{C}$  so that the membrane just touched the receptor medium surface. The dissolution medium was stirred at low speed using magnetic stirrer. An aliquot of 5ml of the sample was withdrawn from the receiver compartment at pre-determined time intervals and replenished with fresh medium. Samples were analyzed by UV-Visible spectrophotometer at a wavelength of 376 nm. Data obtained from *in vitro* release studies were fitted to various kinetic equations to find out the mechanism of Lornoxicam release from NLC.

#### In vivo study (Anti-Inflammatory activity) of the promising formulation: [19, 20, 21]

0.3% Carbopol gel was prepared using optimized NLC formulation having 1% w/v lipid concentration.

Animal Ethical clearance certificate was obtained from KLEU's College of Pharmacy, Belgaum by institutional Animal Ethics Committee; reference No KLECOPIAEC/Res.15-07/08/2012, dated 7th August 2012. Rats were divided into four groups containing six rats in each group (n=6). The Anti-Inflammatory activity was conducted on Wister rats, six per group divided in four groups, of either sex, weighing 180 $\pm$ 20 g. The first group served as control and received normal saline. The second group was disease control. Inflammation was induced by injecting carrageenan. Optimized formulation NLC based carbopol gel was administered to third group. The fourth group received Lornoxicam by oral route. The change in edema volume of the rat hind paw was measured by using a mercury plethysmometer. Lornoxicam gel was applied to the planter surface of the right hind paw by gently rubbing 50 times using the index finger. After 1 hr, 0.1 ml of 1% carrageenan suspension in sterile normal saline was injected subplantarily into II to IV rat groups and the paw volume was again measured up to 6hrs. The percent swelling of the paw was determined using the formula

$$\frac{V_i - V \times 100}{V}$$

Percent swelling =

Where, V is the paw volume after the carrageenan injection,

$V_i$  is the initial paw volume.

### RESULTS AND DISCUSSION

Nanostructured lipid carrier of Lornoxicam was successfully prepared by hot homogenization method. This technique presents

numerous advantages. It is a straight forward technique, rapid and easy to perform.

Hot homogenization method is carried out by rapid melting of the lipid. As the lipid containing mixture was melted, the drug was added followed by addition of the surfactant solution drop wise for drug entrapment.

### FTIR studies

FT-IR spectroscopy was carried out to study the compatibility of pure drug Lornoxicam with the lipid Compritol ATO 888 used in the formulation of nanostructured lipid carrier. The pure Lornoxicam has characteristic IR peaks at 3433.29  $\text{cm}^{-1}$  (aromatic N-H stretch), 1645.28  $\text{cm}^{-1}$  (aromatic C=O stretch), 1085.92  $\text{cm}^{-1}$  (S=O stretch), 3066.82  $\text{cm}^{-1}$  (aromatic C-H stretch), 1537.27  $\text{cm}^{-1}$  (aromatic C=C stretch), 1327.03  $\text{cm}^{-1}$  (C-N stretch) and 630.72  $\text{cm}^{-1}$  (C-Cl stretch) as depicted in (Fig. 1). Compritol ATO 888 has a characteristic IR absorption frequency at 1732.08  $\text{cm}^{-1}$  (C=O stretch) and 3064.89  $\text{cm}^{-1}$  (C-H stretch), depicted in (Fig. 2).

The IR spectra of the physical mixture of both exhibited all the characteristic peaks of Lornoxicam and Compritol ATO 888 as depicted in (Fig. 3). Therefore, it shows compatibility of Lornoxicam with Compritol ATO 888.

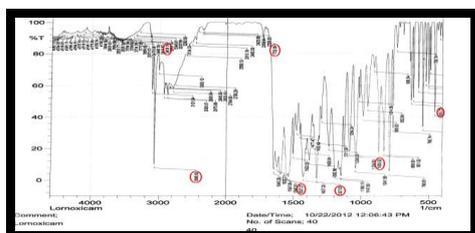


Fig. 1: FT-IR of Lornoxicam

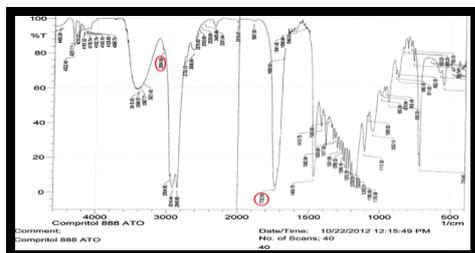


Fig. 2 : FT-IR of Compritol ATO 888

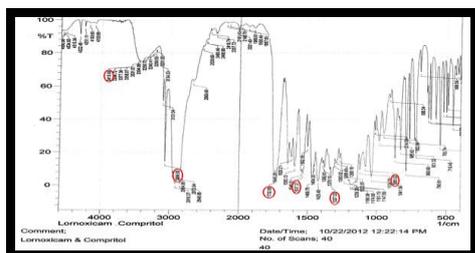


Fig. 3: FT-IR of physical mixture of Lornoxicam and Compritol ATO 888

### DSC Analysis

DSC study has been widely used as a rapid thermal method for examining the drug-excipient compatibility because this method is fast and uses only few milligrams of the sample. DSC curves of Lornoxicam and mixture of Lornoxicam and Compritol ATO 888 were obtained. The results of DSC are shown in (Fig. 4 and 5).

Pure Lornoxicam showed a sharp exothermic peak at 222.04°C which corresponds with the melting point of Lornoxicam and an associated fusion enthalpy of 138.15 J/g. The DSC curve of the

physical mixture showed a sharp endothermic peak at 73.49°C corresponding to melting point of Compritol ATO 888 and fusion enthalpy of -62.53 J/g, followed by the exothermic peak of Lornoxicam at 222.04°C and fusion enthalpy -6.61 J/g. DSC curves of lornoxicam and physical mixture showed curves at characteristic melting point of Lornoxicam. Therefore, Lornoxicam shows compatibility with Compritol ATO 888 upon subjecting to heat.

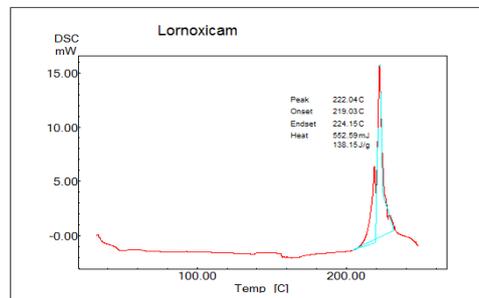


Fig. 4: DSC of Lornoxicam 888

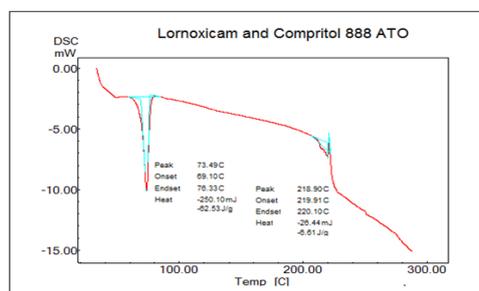


Fig. 5: DSC of Lornoxicam and Compritol ATO 888

### Particle Size Analysis [22]

Particle size of the nanoparticles is presented as z-average diameter, which is basically mean hydrodynamic diameter of the particles. Particle size measurement was required to confirm the production of the particles in nano-range. Particle size data for the Nanostructured lipid carriers of Lornoxicam is shown in (Table 2).

The mean particle size for formulations LF1 to LF8 varied in range of 64.60 to 440 nm. NLC prepared from lipid to surfactant ratio 1:1 showed significantly lowest particle size (64.60nm) and NLC with lipid to surfactant ratio 2.5:1 showed highest particle size (440nm). The particle size analysis reveals that the size reduction was due to speed. As the lipid concentration was increased, more particles were aggregated resulting in an increased particle size. When the concentration of the lipid exceeded 2.5% w/v with a fixed concentration of surfactants, there was insufficient surfactant available to coat the surface of all the lipid droplets, resulting in particle aggregation and an increase in particle size.

### Polydispersity index [23]

Polydispersity index (PI) indicates the width of the particle size distribution, which ranges from 0 to 1. A monodisperse sample indicates PI value nearer to 0. However, PI < 1 indicates polydisperse samples. Therefore, PI measurement was essential to confirm the size distribution of the particles.

The mean polydispersity index values for the drug loaded NLC formulations varied in the range of 0.134 to 1.02 as tabulated in (Table 2). It could be inferred that all the formulations showed polydispersity.

### Entrapment efficiency

The experimental results indicate that the concentration of lipid has critical effect on the Lornoxicam incorporation efficacy. The entrapment efficiencies of NLC made from different concentrations of lipid carrier are in the ascending order. The reported reasons for that are entrapment efficiency is lower for the sample with lower

lipid concentration. The values of drug entrapment efficiency are shown in (Table 2).

The entrapment efficiency was found to be in the range of 79.5% to 89.06%. The maximum entrapment efficiency (89.06%) was found for LF8 with 2.5% w/v lipid concentration whereas it was less (79.50%) for LF5 with 1% w/v lipid concentration.

A higher concentration of lipid causes increase in the particle size that would affect the amount of Lornoxicam adsorbed on the surface of NLC. This is reasonable as higher amount of lipid was available to encapsulate drug molecules at higher lipid concentration.

**Table 2: Characterization of nanostructured lipid carrier of Lornoxicam**

Formulations	Mean Particle size (nm)*	Polydispersity Index (%)	Drug Content (mg)*	%EE
LF1	365±3.20	0.588	14.01±1.59	87.56
LF2	280.8±20.53	0.662	13.82±1.05	86.38
LF3	117.6±3.94	0.672	13.21±1.24	82.56
LF4	84.10±9.57	0.933	12.84±1.19	80.25
LF5	64.60±10.22	0.802	12.72±1.79	79.50
LF6	114.5±3.26	0.62	12.99±1.26	81.19
LF7	325±0.0600	0.134	14.11±1.22	88.19
LF8	440±5.08	1.02	14.25±1.18	89.06

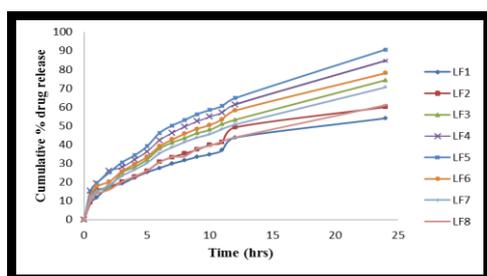
\*Data are expressed as Mean ±S.D. (n=3),

%EE - % Entrapment Efficiency

#### **In vitro drug release**

The profiles were biphasic, with an initial burst of drug release attributed to surface associated drug, followed by a phase of slower release as drug entrapped inside the particle diffused out in to the release medium (Fig. 6).

Particle size has a direct effect on the drug release profile. Formulation LF5 with small particle size (64.60 nm) gave large initial burst release of 25.17% after 2 hrs and 90.67% release after 24 hrs. Formulation LF8 (particle size 440 nm) and LF1 (particle size 365 nm) with larger particle gave small initial burst release of 16.01% and 17.64 after 2 hrs and 61.01% and 54.04% release after 24 hrs respectively. There is a relation between drug release and the mean particle size for NLC release study. The smaller particles have a higher surface area which gives the more initial burst release and hence prolonged sustained release.

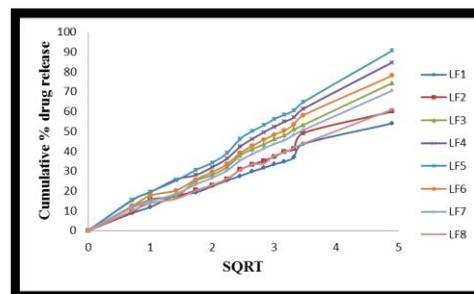


**Fig. 6: In vitro drug release of LF1-LF8 formulated batches**

#### **In vitro drug release kinetics**

The release data were fitted to various kinetic models in order to calculate the release constant and regression coefficients ( $R^2$ ).

Among the models tested, the drug release profiles for formulations (LF1 to LF8) were best fitted with Higuchi Matrix model based on regression coefficients (0.9902, 0.9834, 0.9943, 0.9944, 0.9964, 0.9943, 0.9962 and 0.9956 respectively). The linearity of the plot indicated that the release process was diffusion controlled. Thus, the amount of drug released was dependant on the matrix drug load. The diffusion exponent (n) values for all formulations were less than 0.5, indicative of fickian mechanism of drug release.



**Fig. 7: Comparative Higuchi Matrix plots of formulations LF1 to LF8**

#### **Zeta ( $\zeta$ ) potential [23]**

$\zeta$  Potential is an important parameter to analyze the long-term stability of the nanoparticles. Zeta potential (ZP) refers to the surface charge of the particles. ZP ( $\pm$ ) indicates the degree of repulsion between close and similarly charged particles in the dispersion. This repulsion force prevents aggregation of the particles. Therefore, ZP is a useful parameter to predict the physical stability of the NLC dispersions. Zeta potential is the most important parameter for physical stability of nanoparticles. The higher the electrostatic repulsion between the particles the greater is the stability. ZP value more than +20 mV or less than -20 mV predicts good physical stability of nanoparticle dispersion.

The  $\zeta$  Potential value of optimized formulation LF5 was found to be -25.2 mV. It predicts good particle stability because the repulsive forces prevent aggregation with aging.

#### **In vivo studies of the optimized NLC (LF5) formulation of Lornoxicam carbopol gel**

The anti-inflammatory activity of optimized NLC formulation of prepared Lornoxicam Carbopol gel was tested against carrageenan induced inflammation. At the 6<sup>th</sup>hr the % swelling was found to be 48.77% for NLC formulated Carbopol gel and 46.27% for oral administration of lornoxicam. The % swelling inhibition of the formulation was found to be 44.39% at 5<sup>th</sup>hr and 48.77% at 6<sup>th</sup> hr.

#### **CONCLUSION**

Nanostructured lipid Carriers were prepared using Compritol ATO 888, Medium chain triglycerides and polaxomer 188. FTIR and DSC studies of Lornoxicam, Compritol ATO 888 and their physical mixture confirmed that there was no significant interaction between them. The particle size of the prepared NLC was suitable for topical administration (below 500nm). The mean hydrodynamic diameter of the particle and entrapment efficiency increased with increase in the lipid concentration. Lornoxicam release kinetics was dependent upon the size of the nanoparticles. The larger particles showed slow *in vitro* release whereas the small particles exhibited a faster release. *In vitro* release study was analyzed using various mathematical models. The regression co-efficient of Higuchi matrix suggests linearity and n value of Peppas model was less than 0.5 suggests Fickian diffusion mechanism of drug release. Formulation LF5 containing 1% lipid was the optimized formulation based on its particle size and percentage drug release (% CDR) when compared with other formulations. The Zeta Potential value predicted good particle stability because the repulsive forces prevent aggregation with aging. Carbopol gel was prepared using optimized formulation and tested against carrageenan induced inflammation. After 6 hours the percent swelling inhibition was found to be 48.77%.

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