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# FORMULATION AND EVALUATION OF NANO STRUCTURED LIPID CARRIER (NLC) OF IBUPROFEN FOR THE TREATMENT OF INFLAMMATION

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## ABSTRACT

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID). It works by reducing hormones that cause inflammation and pain in the body. This drug was selected for the study because it has good percutaneous absorption and appears to be more active as anti inflammatory activity and is well tolerated. Nano structured lipid carrier was formulated by high speed homogenization method which was found to be simple and economic. Excipients (lipids) used in the study was economic and safe. In vitro release studies of the formulations were carried out across the dialysis membrane using a diffusion cell. Among all the formulations, the release was highest for the formulation NLC F1 as 98.63% in 12 hours diffusion study. It also shows lowest particle size, better entrapment efficiency and high zeta potential value, hence NLC-IBU F1 was concluded as optimized formulation. The optimized nano structured lipid carrier IBU-NLC formulation was dispersed into gel. The polymers namely Carbopol-940 was used as gelling agent for formulation of gels and studied for their drug permeation from the NLC- gel formulations. Carbopol gels were transparent, non-greasy and smooth on application. The pH of the formulations ranged from 6.5 to 7.1.The spreadability data ranges from 4.3-5.5 gm-cm/sec. The drug content was found to be 90-94%. The pH, spreadability and drug content were good and up to the acceptable range. The in vitro diffusion study of NLC gel formulations were carried out across the skin membrane using Franz diffusion cell. It shows good permeation into skin for prolonged release of 12 hours than the marketed gel formulation.

**Keywords:** Ibuprofen, NanoLipid carrier (NLC), Topical gel, anti-inflammatory

## INTRODUCTION

Osteoarthritis (OA), one the most prevalent chronic joint diseases, is accompanied by considerable pain. Since pain and inflammation are among the most important causes of a decline in the life quality, the primary aim of the currently available treatments is to relieve these pain.[1,2] The American College of Rheumatology has published recommendations for the use of nonpharmacologic and pharmacologic therapy in OA. The use of nonsteroidal anti-inflammatory drugs is highly recommended. The low bioavailability of oral and systemic forms of ibuprofen coupled with side effects necessitates the need to explore topical administration.

The Ibuprofen drug, usually administered in its racemic form, is a first line anti-inflammatory drug is relatively lipophilic (log P=4.0) with low water solubility (21 mg/L at 25°C).Earlier studies revealed that the topical therapeutic effectiveness of a drug is a function both of its penetration through the skin and of its potency. The aforementioned physicochemical properties of IBU have hampered the preparation of a formulation satisfying the requirements of a long-lasting treatment for a chronic disease such as OA.[3-6] Topical deliveries provide an increased bioavailability by avoiding first pass metabolism by the liver and a consistent delivery for an extended period. Topical delivery vehicles (creams, gels) can improve patient compliance due to decrease in the dosage frequency. The advantages of its local application over their systemic use include the avoidance of adverse effects and to provide relatively consistent drug levels at the application site for prolonged periods.

In turn solid lipid nanoparticles (SLN) of ibuprofen showed drug leakage after 45 days of storage. Nanostructured lipid carriers (NLCs) may serve as a solution to overcome the

limitations of the SLN.NLCs can comprise physiological and biodegradable lipids, which were earlier reported to possess low systemic toxicity and low cytotoxicity[7,8]. The small size of the lipid nanoparticles ensures close contact between the lipid particles and the lipid bilayerof the stratum corneum, resulting in the penetration of an increased amount of drug into the skin. The solid lipid, when used alone for preparing SLNs, forms a perfect crystal lattice with limited space for accommodating the drugs. In NLC both solid lipid and liquid lipid was included in formulation which allows more space to accommodate drug and increases the solubility of drug.[9,10]So, Nano structured lipid carrier could be a great way to ensure that the compounds are delivered efficiently and effectively to the desired area of the body.

## EXPERIMENTAL METHODS

### Preparation of ibuprofen loaded NLC gel

Carbopol was selected as the gelling agent. The composition of gel formulation are mentioned in **Table 1**. The required amount of Carbopol was dispersed in the water and allowed to hydrate for 4 to 5 hour. Glycerine (10% w/w) used as humectants was added subsequently to the aqueous dispersion using a mechanical stirrer (Remi, Mumbai, India) at a speed of 1200 rpm for 1 hour. The dispersion was neutralized using triethanolamine. The gel was allowed to stand overnight to remove entrapped air.

**Table 1: Composition of NLC based gel formulations**

| Sl .no | Ingredients (%w/w) | Formulation |
|---|---|---|
| | | IBU- NLC gel (%w/w) |
| 1 | Carbopol 940P | 1 |
| 2 | Glycerine | 10 |
| 3 | Triethanolamine | 0.5 |
| 4 | Distilled water | 88.5 |
| 5 | Methyl paraben | 0.002 |

The gel was formulated as given in above table 9 . IBU-NLC (equivalent to ibuprofen 5%w/w) was dispersed into the gel. All NLC formulations were formulated as gel in the same composition as given in **table 1** and evaluated.

## CHARACTERIZATION OF NLC

### Particle size and zeta potential

The mean particle size and zeta potential of the IBU-loaded NLC formulations were determined using Malvern® Zetasizer Nano ZS90 (Malvern® Instruments Limited, Worcestershire, UK). All the measurements were made in triplicate after dilution (1:200) with distilled water at room temperature using 90° scattering angle.

### Scanning electron microscopy

The shape and surface characteristics of NLCs were determined by SEM using gold sputter technique (ZEISS EV40, Carl Zeiss NTS, North America). Samples of NLC were dusted onto a double-sided tape on an aluminum stub. The stubs containing the sample were coated with gold using a cool sputter coater (Polaran E 5100) to a thickness of 400 A0. Photomicrographs were taken at the accelerated voltage of 20 kV and chamber pressure of 0.6 mmHg.

### Drug encapsulation efficiency

Drug encapsulation efficiency (EE) was determined through indirect method where an aliquot (2 ml) of Ibuprofen-loaded NLCs was centrifuged at 10,000 g for 2 h at 4 °C. The proportion of unencapsulated ibuprofen in the clear supernatant fluid was measured spectrophotometrically at 264 nm against blank. Calibration curve for the validated UV assay of Ibuprofen was performed on six solutions in the concentration ranges of 2–16 µg/ml. Correlation coefficient was >0.999. Each point represents the mean of three measurements and standard deviation (±SD) was calculated. The encapsulation efficiency of Ibuprofen was then calculated according to the following equation

$$EE\% = (Da-Df / Da)x\ 100$$

where EE%= the percentage of encapsulation efficiency,
Da = the amount of added drug during preparation of NLCs and
Df = the amount of free drug in the clear supernatant fluid after centrifugation.

### In vitro drug diffusion study

In vitro release studies were performed using a modified Franz diffusion cell. Dialysis membrane having pore size 2.4 nm and molecular weight cut-off between 12,000 and 14,000 was used. The membrane was soaked in double distilled water for 12 h before mounting in a Franz diffusion cell. About 0.5 g of NLC formulation was applied to the donor compartment, and the receptor compartment was filled with phosphate buffer, pH 7.4 (5 mL). During the experiments, the solution in the receptor side was maintained at 37 ± 0.5 °C and stirred at 100 rpm with Teflon-coated magnetic stirring bars . At various time intervals such as 1,2,3,4,5,6,7,8,9,10,11,12 hour , 1 mL of the sample was withdrawn from the receiver compartment through a side tube and analyzed spectrophotometrically at 264 nm.

# RESULTS & DISCUSSION

## Results for preformulation studies

## Solubility studies

The solubility shows that the drug was lipophilic in nature and the drug was freely soluble in organic solvents and soluble in phosphate buffer (7.4).

**Table 2: Result of solubility study**

| Sl no | Solvents | Results |
|---|---|---|
| 1 | Acetone | +++ |
| 2 | Phosphate buffer solution | ++ |
| 3 | Water | -- |
| 4 | Chloroform | +++ |
| 5 | Methanol | +++ |
| 6 | Ethanol | +++ |

Insoluble = --
Soluble = ++
Freely soluble = +++

## *λ*-max

The ***λ*-max** value was found as 264 nm when scanned in U-V Spectrophotometer in the range of 200-400 nm.

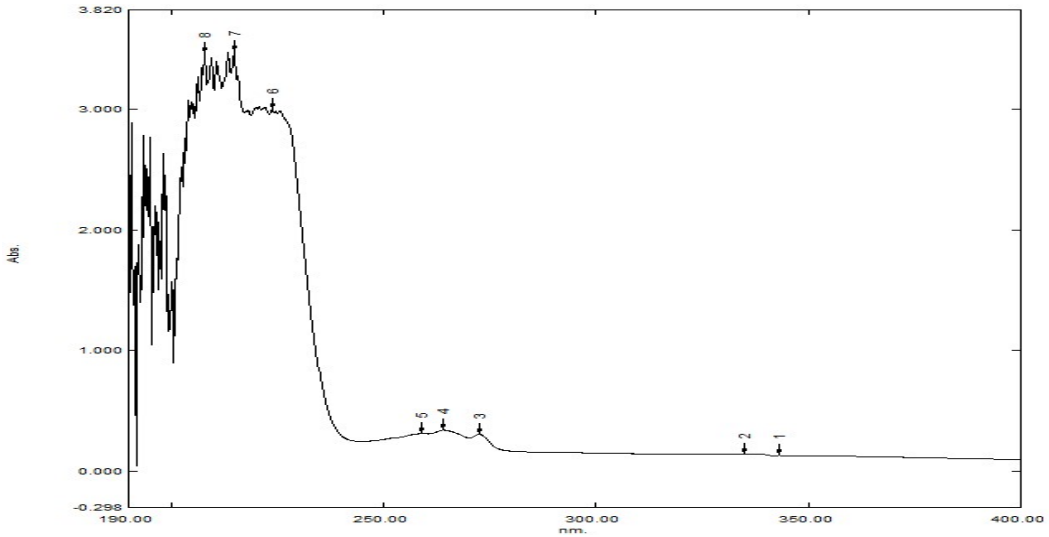



**Figure 1: *λ*-max curve of Ibuprofen.**

## Partition coefficient

The log P value was found as 3.227
The log S value was found as-3.287 when calculated using yalkowsky and banerjee equation.

**Log S= 0.8-Log $P_{o/w}$ -0.01(MP-25)**
Where,
S-solubility
Log $P_{o/w}$ -octanol/water partition coefficient
MP-melting point ($76^0$C)

The log p and log S value for ibuprofen drug was found to be 3.227 and -3.287 which was found to be same as compare to standard ibuprofen drug. The standard ibuprofen drug was found to be 3.97 for log p and -3.99 for log S.A positive value for logP denotes a higher concentration in the lipid phase (i.e., the compound is more lipophilic). The negative value for log S indicates poor absorption.

## Calibration curve

The calibration curve of drug obeyed Beer Lambert's law in the concentration range of 0-16µg/ml ($R^2$ = 0.999) and result shown in figure2.

**Table 3 : Calibration curve of Ibuprofen**

| CONCENTRATION (MCG) | ABSORBANCE (NM) |
|---|---|
| 4 | 0.045 |
| 6 | 0.058 |
| 8 | 0.071 |
| 12 | 0.098 |
| 16 | 0.125 |

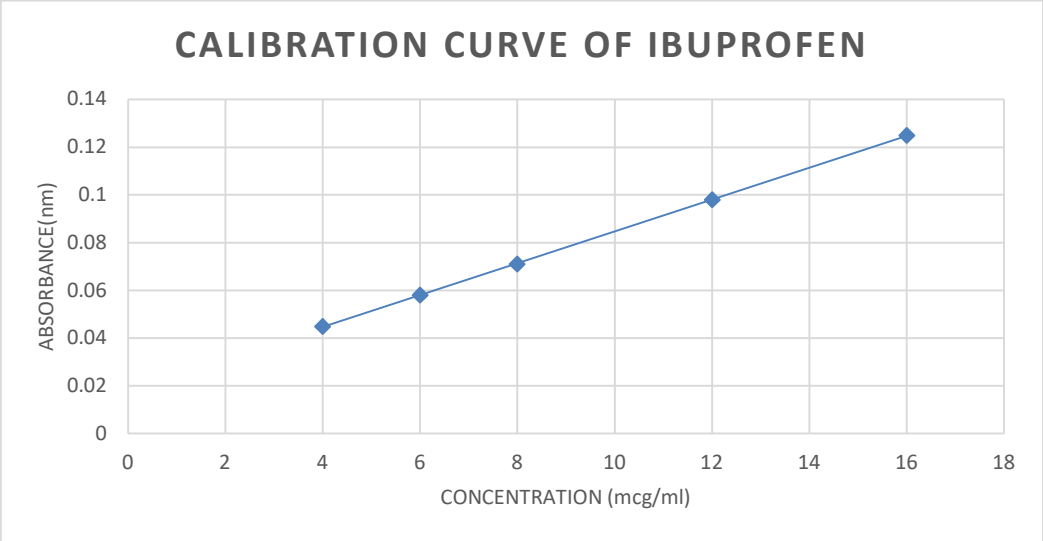



**Figure 2: Calibration curve of Ibuprofen**

## Compatibility study by FTIR

The FTIR spectra of pure ibuprofen, solid lipid (glycerylmonostearate) and the NLC formulation shown in Fig. 3,4 and 5 respectively. The IR spectra of the pure drug show principle peaks at 1721.21 cm-1 (C= O stretching Vibrations of - COOH group), 866.21, 779.58 cm-1 (Aromatic stretching bending vibration). The formulation shows peaks at 1740.49 and 2955.96. Likewise, the solid lipid shows peak at 2955.89 and 1739.62. Thus it concluded that the physical mixture of the drug ibuprofen does not show any major interactions with formulation components like solid lipid (glycerylmonostearate).

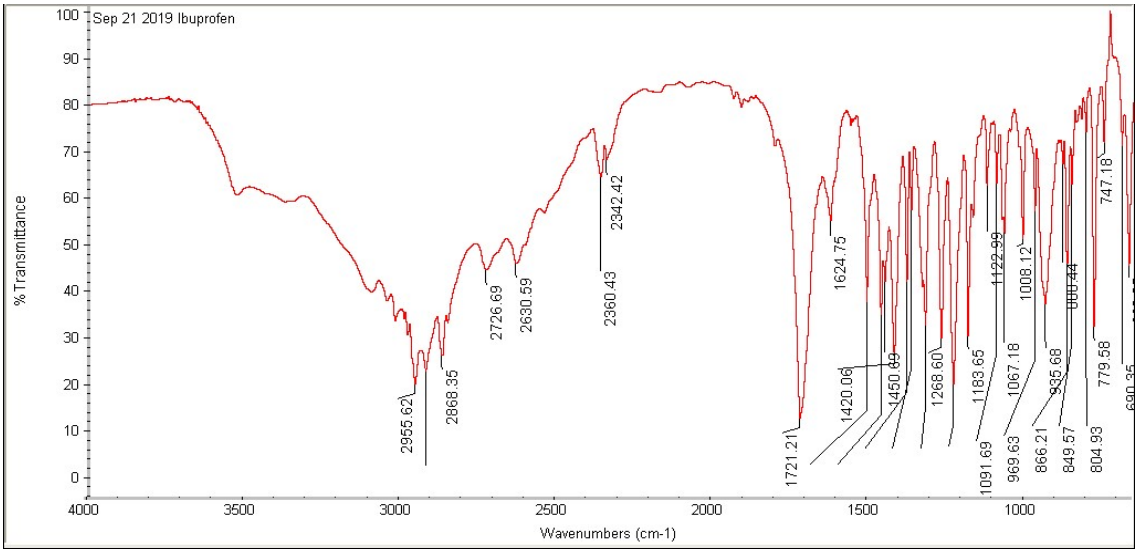



**Figure 3: FTIR graph of pure drug (Ibuprofen)**

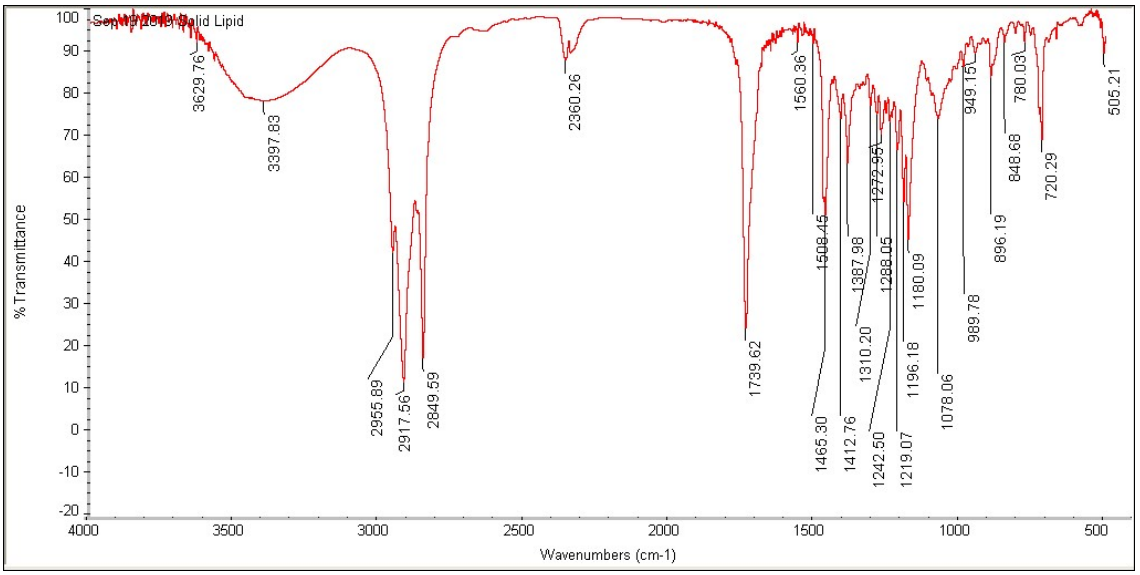



**Figure 4:FTIR graph of solid lipid (glycerylmonostearate)**

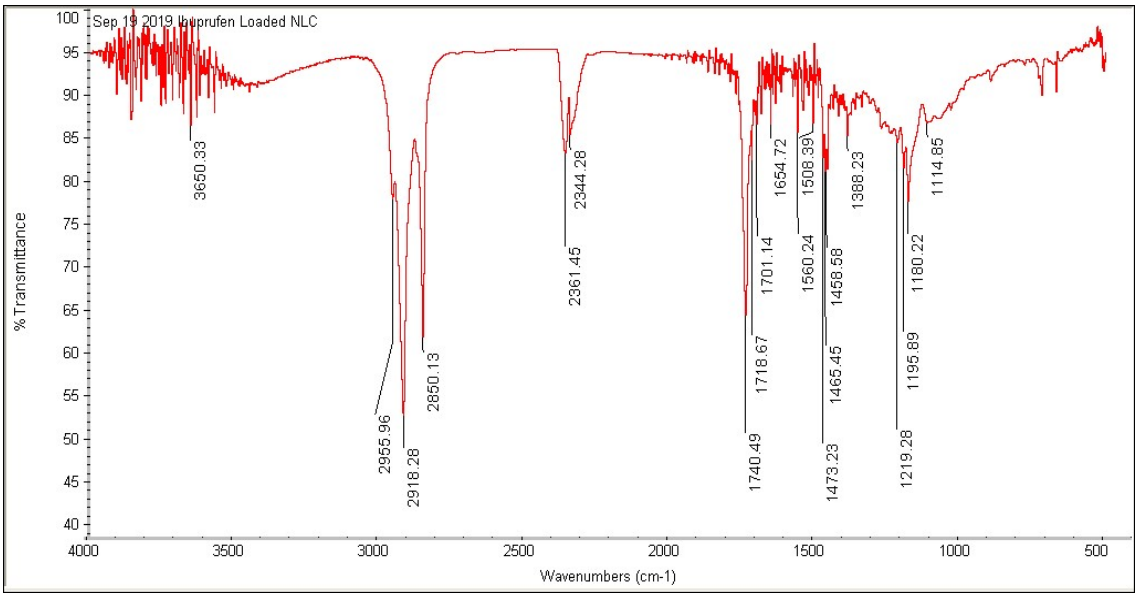



**Figure 5:FTIR graph of ibuprofen loaded NLC(F1)**

## Evaluation of Ibuprofen loaded NLC

### Particle size

The particle size and zeta potential was determined using Malvern Mastersizer.The particle sizes of formulation, increases when the concentration of solid lipid increases. The particle size of sample was found to be 193.6 nm. Zeta potential was found to be -44.4, it indicates that the surface charge was negative and obtained results shown in figure 18. It is known that ZP values of more than ±30 are considered as a good indication for the stability of the nano structured lipid carrier[49]. The small particle size indicates the formulation contain greater interfacial area, which will provide better drug partitioning and absorption at the skin surface.

# Size Distribution Report by Intensity

*v2.2*

Malvern

## Sample Details

**Sample Name:** W Gel 1

**SOP Name:** mansettings.nano

**General Notes:**

| | | | |
|---|---|---|---|
| **File Name:** | DLS RESULTS 2019.dts | **Dispersant Name:** | Water |
| **Record Number:** | 464 | **Dispersant RI:** | 1.330 |
| **Material RI:** | 1.33 | **Viscosity (cP):** | 0.8872 |
| **Material Absorbtion:** | 0.101 | **Measurement Date and Time:** | Monday, September 30, 20... |

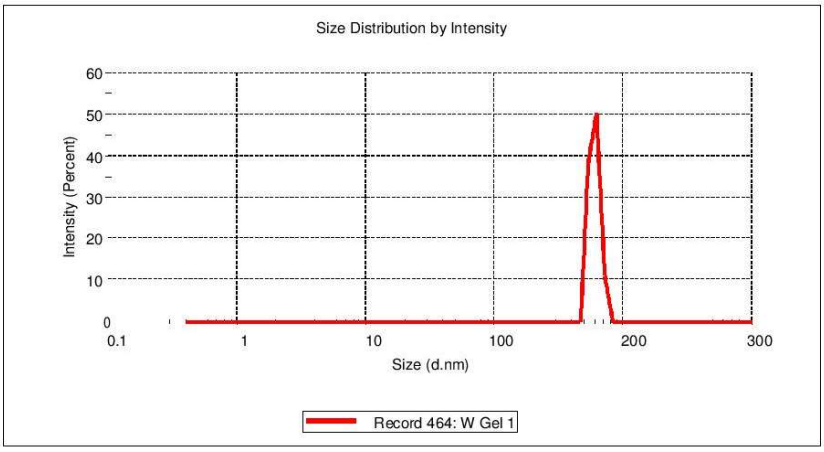
## System

| | | | |
|---|---|---|---|
| **Temperature (°C):** | 25.0 | **Duration Used (s):** | 80 |
| **Count Rate (kcps):** | 145.0 | **Measurement Position (mm):** | 4.65 |
| **Cell Description:** | Disposable sizing cuvette | **Attenuator:** | 7 |

## Results

| | | Size (d.nm... | % Intensity: | St Dev (d.n... |
|---|---|---|---|---|
| **Z-Average (d.nm):** 163.8 | **Peak 1:** | 193.6 | 100.0 | 57.41 |
| **PdI:** 0.461 | **Peak 2:** | 0.000 | 0.0 | 0.000 |
| **Intercept:** 0.989 | **Peak 3:** | 0.000 | 0.0 | 0.000 |

**Result quality** **Refer to quality report**



# Zeta Potential Report

*v2.3*

Malvern



## Sample Details

**Sample Name:** w gel 1

**SOP Name:** mansettings.nano

**General Notes:**

| | | | |
|---|---|---|---|
| **File Name:** | DLS RESULTS 2019.dts | **Dispersant Name:** | Water |
| **Record Number:** | 465 | **Dispersant RI:** | 1.330 |
| **Date and Time:** | Monday, September 30, 2019 ... | **Viscosity (cP):** | 0.8872 |
| | | **Dispersant Dielectric Constant:** | 78.5 |

## System

| | | | |
|---|---|---|---|
| **Temperature (°C):** | 25.0 | **Zeta Runs:** | 10 |
| **Count Rate (kcps):** | 173.1 | **Measurement Position (mm):** | 2.00 |
| **Cell Description:** | Clear disposable zeta cell | **Attenuator:** | 6 |

## Results

| | | | Mean (mV) | Area (%) | St Dev (mV) |
|---|---|---|---|---|---|
| **Zeta Potential (mV):** | -41.6 | **Peak 1:** | -44.4 | 84.5 | 7.69 |
| **Zeta Deviation (mV):** | 10.4 | **Peak 2:** | -23.5 | 15.5 | 4.08 |
| **Conductivity (mS/cm):** | 0.0108 | **Peak 3:** | 0.00 | 0.0 | 0.00 |
| **Result quality** | See result quality report | | | | |

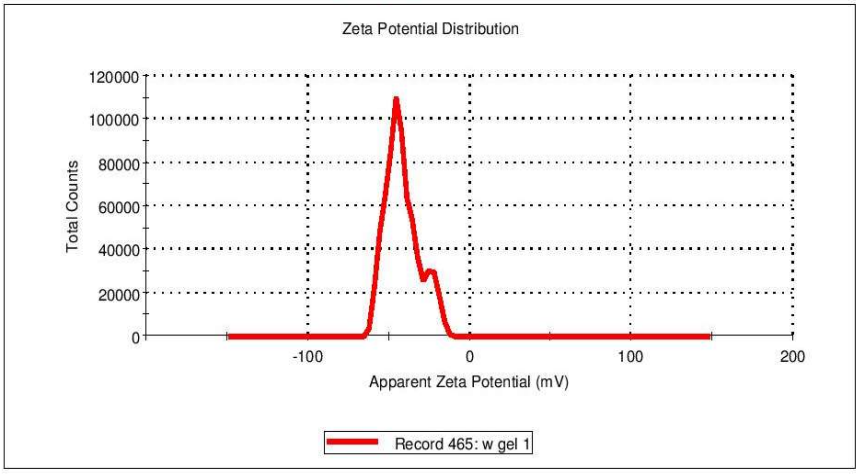





**Figure 6: Particle size distribution and zeta potential**

## Scanning electron microscopy

Surface analysis of Ibuprofen loaded nano structured lipid carrier was carried out by Scanning Electron Microscopy. Images obtained after SEM are shown in Figures 19 for F1, F3 and F6. Among all the formulations, F1was spherical in shape. F1 have spherical- shape, and fine- smooth surface because of optimum concentration of solid and liquid lipid.

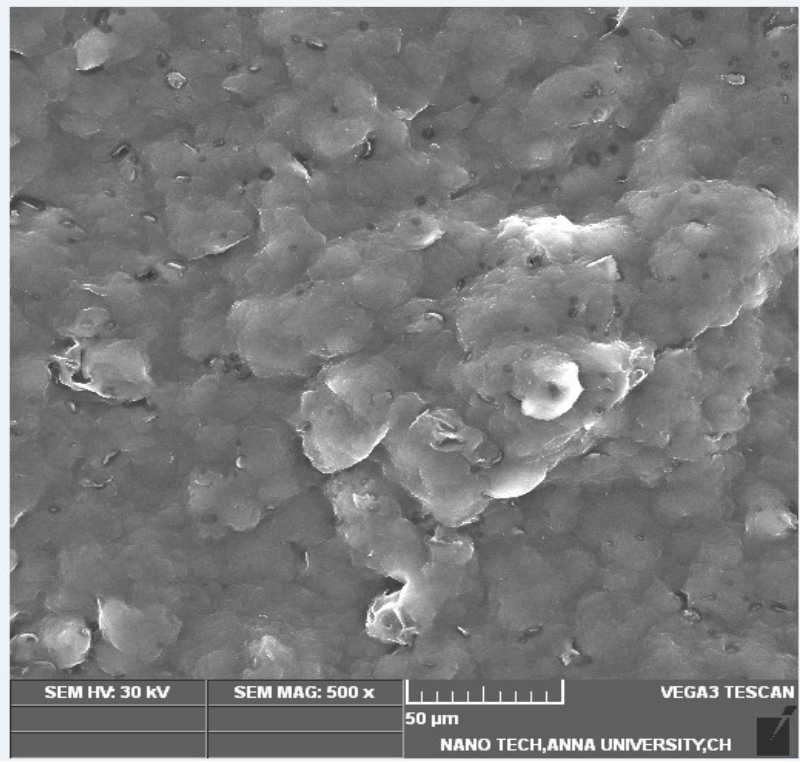



**Figure 7: SEM images of NLC formulations**

## Entrapment efficiency

The nano structured lipid carrier were prepared by different proportions of Drug, glyceryl monostearate, and surfactant. The entrapment efficiency of nano structured lipid carrier loaded Ibuprofen increases with increase in the concentration of glyceryl monostearate and Tween 80. The entrapment efficiency found in the range between 73.9% to 89.00%. Formulation (F1 and F3) of NLC has shown maximum entrapment (that is 89.00% and 85.50%) as the concentration of lipid increases, while Formulation (F4 and F6) of NLC has shown lowest entrapment that is (74.00% and 73.90%) as the concentration of solid lipid decreases. High lipophilicity of Ibuprofen resulted in high entrapment efficiency of drug in triglyceride nanoparticles. This might be because of the long-chain fatty acids attached to the glyceride resulting in increased accommodation of lipophilic drugs . The less ordered lipid matrix created imperfections leading to void spaces in which drug molecules could be entrapped . In the method of preparation, drug was dissolved in molten lipid at temperature above the melting point of lipid and there was no drug leakage or precipitation of drug during the preparation. High encapsulation efficiency of drug in lipid nanoparticles can cause high amount of drug to pass through the lymphatic transport.

## In vitro diffusion study

In vitro release of Ibuprofen from IBU-NLCs was studied in pH 7.4 phosphate buffer by dialysis membrane method. In pH 7.4 phosphate buffer, the cumulative % of release from formulations F1-F6 was 98.63%, 65.84%, 74.65%, 84.25%, 85.23% and 65.22% respectively in 12 hours (table 21,22,23,24,25,26). The release profiles of NLC formulations exhibited a typical biphasic pattern with an initial rapid phase followed by a slow phase in phosphate buffer. The initial rapid phase could be due to the burst release of drug. A possible explanation is a short diffusion path due to enrichment of drug in the outer region of NLC or drug deposition on the solid surface. Among other formulation, F1 was obtained as best formulation because it contains 65% solid lipid and 15% of liquid lipid makes a perfect nanostructured lipid carrier. Formulation F1 showed maximum release of 98.63% in pH 7.4 phosphate buffer during 12 hours. In comparison with other formulations, F1 exhibited reasonably good particle size, high zeta potential value, and the higher entrapment efficiency with release of drug from the lipid matrix in pH 7.4 phosphate buffer, hence it was considered as the optimized formulation.

During the formulation, the solubility of the drug is increased when the temperature increases (70°C–80°C) in the presence of a surfactant in the aqueous phase. During the cooling phase, the drug is repartitioned into the lipid phase, and the solid lipid recrystallizes and forms a solid lipid core. Greater amounts of the drug are entrapped in the core lipid matrix and lower amounts of the drug are deposited at the shell and/or the surface of the lipid nanoparticles. Therefore, the formulation contains less amount of drug on the surface and the outer shell of the IBU-NLC contributes to the initial

fast release; moreover, the drug present in the core of the lipid matrix contributes to the second slow release phase. During the solidification at a low temperature, due to the solid lipid (GMS) owning a higher melting point, it would rapidly solidify to form a solid lipid core in which liquid lipid was randomly distributed. When the liquid lipid (Coconut oil) content is higher, liquid lipids would be located at the outer shell of the nanoparticles besides being distributed in the solid lipid core, which led to drug-enriched shell related with drug burst release at the initial stage. In addition, as liquid lipid was distributed in solid lipid, the crystalline structure of NLC became more imperfect and allowed drugs loaded to release more easily, thus increasing the rate of drug release.

In vitro release of Ibuprofen from IBU-NLCs formulations F1,F2,F3,F4,F5,F6 and Ibuprofen suspension was studied in pH 7.4 phosphate buffer by dialysis membrane method. In pH 7.4 phosphate buffer, the cumulative % of release from ibuprofen suspension was found to be 29.66 % respectively in 12 hours. The suspension dissolves more quickly because of large surface area obtained for diffusion. The amount of ibuprofen diffused from the IBU NLC after 12 hours was significantly higher (98%) than the IBU suspension. IBU-NLCs showeda biphasic drug release pattern was observed, that was drug burst release at the initial stage and followed by sustained release at a constant rate.

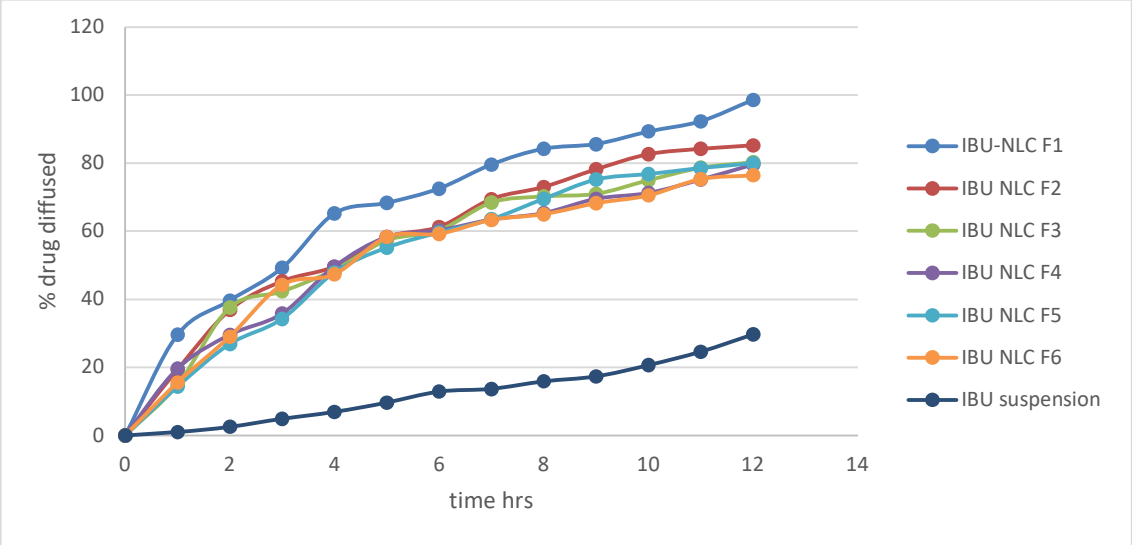



**Figure8 : Comparative in vitro study of suspension and IBU-NLC formulations.**

## CONCLUSION

The present work describes a study on preparation and in vitro evaluation of ibuprofen loaded nano structured lipid carrier (NLC). It is evidence from the FTIR spectrum shows that the lipids (solid lipid ) used in the NLC formulations were compatible with the drug Ibuprofen.From this investigation, it was concluded that formulation F1 was concluded as best formulation. It could be concluded that NLCs may play an important role in controlling the release of Ibuprofen from NLCs as well as targeting of drug to the skin. The amount of drug retained in the skin for NLC based gel was found to be significantly higher as compared to marketed formulation. The dermal retention of Ibuprofen was attributed to the increased contact with corneocytes, skin occlusion and sustained release owing to the properties of NLCs. Due to their small particle size,NLC make closer contact with the superficial junctions of corneocytes clusters and furrows present between corneocyte islands and favour accumulation for several hours , allowing sustained drug release. Therefore, it can be concluded that the Ibuprofen NLCs gel formulation can be used to extend the duration of drug release and as an efficient topical drug delivery carrier for chronic treatment of inflammation .

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