PREPARATION AND CHARECTERISATION OF TOPICAL NANOEMULSION OF MELOXICAM

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Abstract: The study aimed to develop a topical Nanoemulsion of meloxicam to enhance solubility and minimize oral side effects, thereby improving local bioavailability and patient compliance. Nanoemulsion, with their fine droplet sizes and stability, offer a promising platform for efficient drug delivery. Various formulations were prepared using a spontaneous emulsification technique, each meticulously characterized for physical properties and stability. The nanoemulsions exhibited small droplet sizes ranging from 615 to 1017 nm, with negative zeta potentials ensuring stability during storage and application. Solubility analysis revealed dimethylformamide as an optimal solvent, showcasing complete solubility of meloxicam. The formulations maintained a slightly acidic pH suitable for skin application, ensuring minimal irritation. Rigorous stability studies, including heating-cooling cycles and centrifugation tests, confirmed the formulations' robustness and suitability for long-term storage, crucial for pharmaceutical products. Additionally, freeze-thaw stress tests further validated their stability under accelerated aging conditions. UV-visible spectrophotometry enabled precise measurement of drug content, ensuring uniform dosing across formulations. Overall, the developed meloxicam nanoemulsion presents a promising platform for topical drug delivery, offering enhanced solubility, stability, and potential therapeutic efficacy. This novel formulation holds considerable promise for improving the management of conditions such as rheumatoid arthritis, where localized treatment is essential for optimal therapeutic outcomes while minimizing systemic side effects.

Keywords: Nanoemulsion, Nanoparticle, Rheumatoid Arthritis, emulsion

INTRODUCTION:

Nano emulsions, also known as nanometric-sized emulsions, are fine water-in-oil (w/o) and oil-in-water (o/w) dispersions of two immiscible fluids, as opposed to the milky-white hue concomitant with coarse dispersion. These 20–200 nm droplets are stabilized by adding the appropriate amphiphilic emulsifiers or emulsifiers. Consequently, Nano emulsions are also known as mini-emulsions. Due to kinetic stability, Nano emulsions (NE) are stable on heterogeneous systems, in contrast to micro emulsions (ME). Although Nano emulsions are unique due to their extended physical constancy and are also known as “potential thermodynamic stability,” they do not appear to aggregate or flocculate. The history of Nano emulsions can be traced back to the early 20th century when researcher’s first began experimenting with colloidal systems. Initial work focused on macro emulsions and micro emulsions, but it laid the groundwork for the development of Nano emulsions. Nano emulsions as a distinct category of emulsions gained significant attention in the 1990s. Researchers started to explore their unique properties, such as their extremely small droplet sizes, typically ranging from 20 to 200 nanometres. This period marked a shift toward understanding the potential applications of Nano emulsions, particularly in the pharmaceutical and food industries. [1-5]

Advantages of Nanoemulsion Over other dosage forms [6]:

- Eliminates variability in absorption.
- Increases the rate of absorption.
- Helps in solubilizing lipophilic drug.
- Provides aqueous dosage form for water insoluble drugs.
- Increases bioavailability.
- Various routes like topical, oral and intravenous can be used to deliver the product.
- Rapid and efficient penetration of the drug molecule.
- Helps in taste masking.

Currently transdermal delivery is one of the most promising methods for drug application. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliances and minimizes harmful

side effects of a drug caused from temporary over dose and is convenience in transdermal delivered drugs that require only once weakly application. [7]

In spite of meloxicam preferentially activity that inhibits COX-2 (cyclooxgenease-2) over COX-1 (cyclooxgenease-1), in practice it still has highly disturbs gastrointestinal side effects at high doses on long term treatment. Therefore, there is a high requisiteness of to deliver meloxicam by another route to increase its solubility and modifying gastric adverse effect and delivers the drug to the inflammatory site. [8] Rheumatoid arthritis (RA) is a chronic (long-lasting) autoimmune disease that mostly affects joints. RA occurs when the immune system, which normally helps protect the body from infection and disease, attacks its own tissues. The disease causes pain, swelling, stiffness, and loss of function in joints. It affects the lining of the joints, which damages the tissue that covers the ends of the bones in a joint. RA often occurs in a symmetrical pattern, meaning that if one knee or hand has the condition, the other hand or knee is often also affected. It can affect the joints in the wrists, hands, elbows, shoulders, feet, spine, knees, and jaw. RA may cause fatigue, occasional fevers, and a loss of appetite. RA may cause medical problems outside of the joints, in areas such as the heart, lungs, blood, nerves, eyes, and skin.Symptoms of rheumatoid arthritis: RA affects people differently. In some people, RA starts with mild or moderate inflammation affecting just a few joints. However, if it is not treated or the treatments are not working, RA can worsen and affect more joints. This can lead to more damage and disability. At times, RA symptoms worsen in “flares” due to a trigger such as stress, environmental factors (such as cigarette smoke or viral infections), too much activity, or suddenly stopping medications. In some cases, there may be no clear cause. The goal of treatment is to control the disease so it is in remission or near remission, with no signs or symptoms of the disease.

Rheumatoid arthritis can cause other medical problems, such as:

- Joint pain at rest and when moving, along with tenderness, swelling, and warmth of the joint.
- Joint stiffness that lasts longer than 30 minutes, typically after waking in the morning or after
- resting for a long period of time.
- Joint swelling that may interfere with daily activities, such as difficulty making a fist,
- combing hair, buttoning clothes, or bending knees.
- Fatigue – feeling unusually tired or having low energy.
- Occasional low-grade fever.
- Loss of appetite. [9]

Thus, the aim of this investigation is to formulate and evaluate topical Nanoemulsion of meloxicam used topically to increase solubility of meloxicam and decreasing the oral side effect of meloxicam that lead to enhance meloxicam local bioavailability, therapeutic activity and patient compliance

MATERIAL AND METHOD

Material:

Meloxicam supplied by Lexicare Pharma PVT.LTD. Ankleshwar. Ginger Oil were purchased G.K. & Sons (India), Tween 80 were purchased LOBA chemie Thane, Propylene glycol from OZONE International Mumbai. Methanol and ethanol Avantor performance Material India Limited.

The goal of the study titled Development and characterization of drug loaded nanoemulsion formulations is to create and test nanoemulsion that can aaplied on the targeted site that can penetrate and reach to the systematic circulation. While the oral route of administration is preferred for its ease and precision but the meloxicam show the gastrointestinal irritation that why the topical nanoemulsion has be formulate it can easily applied to the site of action

METHOD [10, 11] :

The topical Nanoemulsion is prepared by the spontaneous emulsification technique. At first, Oil phase and aqueous phase were prepared separately on magnetic stirrers based on the design Of experiment process. Oil phase consisted of ethanol and Ginger oil mixture, under constant Stirring (25 ◦C, 1000 rpm), while the aqueous phase contained the mixture of Tween 80, Propylene glycol and purified water prepared under same conditions (25 ◦C, 1000 rpm).The next step was to add the oil phase into the aqueous phase using a peristaltic pump with a Flow rate of 0.2 ml/min. After this, purified water was added to the mixture at a flow rate of 0.3 ml/min to form a Nanoemulsion, then the system was kept under constant stirring at 25 ◦C For 1 h.

Table No. : 01 The Meloxicam Nanoemulsion Formulations.

Sr. No.	Ingredient	Plain-NE (ml)	F1	F2	F3	F4	F5
1	Tween 80	6.9	4.5	4.5	6.9	6.9	**3.5**
2	Propylene Glycol	3.75	3.75	2.75	2.75	3.75	**1.55**
3	Ethanol	3.75	3.75	3.75	4.5	3.75	**4.2**
4	Purified water	3.75	3.75	3.75	3.75	2.50	**3.75**
5	Ginger oil	15	17.25	15.25	15	16	**20**
6	Meloxicam	-	2mg	2mg	2mg	2mg	**2 mg**

All batches were evaluated for above tests and the batch which shows better results was Considered optimized batch and evaluated for further study.

CHARACTERIZATION OF THE PREPARED MELOXICAM NANOEMULSION:

Size measurement [12] :

The samples of 5 ml Nanoemulsion sonicated at the 37 oC for 30 min and measured using ABT- 9000 nanolaser particle size analyser. The average of droplets size and droplets size distribution Diagrams were obtained. All measurements were taken in triplicate.

Clarity and visual appearance:

Appearance and clarity were determined by visual examination of the formulation under light

Against white and black backgrounds. Solubility Analysis: Solubility of meloxicam in different solvents are depicted in table no 17. From the table it is Evident that meloxicam is more soluble in phosphate buffer and dimethyl formamide than that Of other solvents viz.0.1 N HCl and distilled water.

pH estimation (13):

pH estimation One of the high consequential parameters in the evaluation of Nanoemulaion is the pH. The pH values effect on ionization of the drug i.e. ionized and unionized forms of the drug. The human skin is naturally acidic with a normal pH of 4-6. The women have been attested to have more acidic skin than men. The pH of all the Nanoemulsion formulations was tested by dissolving 1ml of Nanoemulsion in 100 ml of distilled water and stored for 2h then use a digital pH meter at room temperature.

Zeta potential (14):

The samples of 5 ml nanoemulsion sonicated at the 37 oC for 30 min.then sample analyse by Zeta potential analyser Negative values of zeta potential of the formulations indicated that the Formulations were negatively charged and higher value of zeta potential of all the formulation Signified stability of the system .

Infrared (IR) spectroscopy:

The IR spectrum of formulated Drug loaded Nanoemulsion was obtained on FTIR spectrometer (Schimadzu FTIR-8400) over the wave number range of 4000 to 400 cm-1 and compared with The reference spectrum.

Thermodynamic stability studies (15):

Heating–cooling cycles:

The intension behind to perform heating- cooling cycles was to Observe the effect of temperature variations on the nanoemulsion stability. Six cycles between 4 and 40 °C were performed with storage at not less than 48 h at each temperature. The Formulations that were found stable at these temperatures were subjected to centrifugation test.

Centrifugation test:

The formulations were centrifuged for 30 min at 2000 rpm and Evaluations were carried out for phase separation, creaming or cracking. Formulations that Were found stable were selected and subjected for freeze- thaw stress test.

Freeze–thaw cycle (accelerated ageing):

The formulations were subjected to three freeze–Thaw cycles at temperatures between −21 and +25 °C and were stored at not less than 48 h at Each temperature. For further studies, formulations that survived thermodynamic stability tests a Were selected.

RESULT AND DISSCUSION

CHARACTERIZATION OF DRUG:

The drug was evaluated based on certain physicochemical parameters and findings of these studies help in formulating a stable drug delivery system to deliver the drug.

Physical description and organoleptic properties:

Meloxicam was characterized for various parameters and the results are shown in Table. All these parameters were found to be in consonance with literature finding.

Table No. 2: Physical description of meloxicam

Sr. No.	Properties	Specifications
1	Colour	Pale yellow
2	Physical form	Crystalline powder
3	Taste	Bitter
4	Odour	Odourless

As evident from the table, the various parameters of drug were in accordance with their respective literature values, as per Indian Pharmacopoeia monograph specifications.

Melting point:

The melting point of the drug meloxicam as observed by melting point apparatus along with the melting point reported in literature is given in the table

Figure No. 1: Melting point of meloxicam

Table No. : 3 Melting point of Meloxicam

Drug Name	Observed	Standard
Meloxicam	241-248°C	242-245 °C

Determination of λ max:

The λ max of Meloxicam was scanned in different solvents like 0.1 N HCl, DMF, and Methanol with a U V spectrophotometer. Further studies were done using one of among these solvent, that's why we selected these solvent shown in Table

Table No. 4: λ max of Meloxicam in different solvents

Sr. No.	Solvent	Observed λmax	Reported λmax
1	0.1N HCL	355.0	356.0
2	Dimethylformide	361.0	364.0
3	Methanol	373.0	375.5

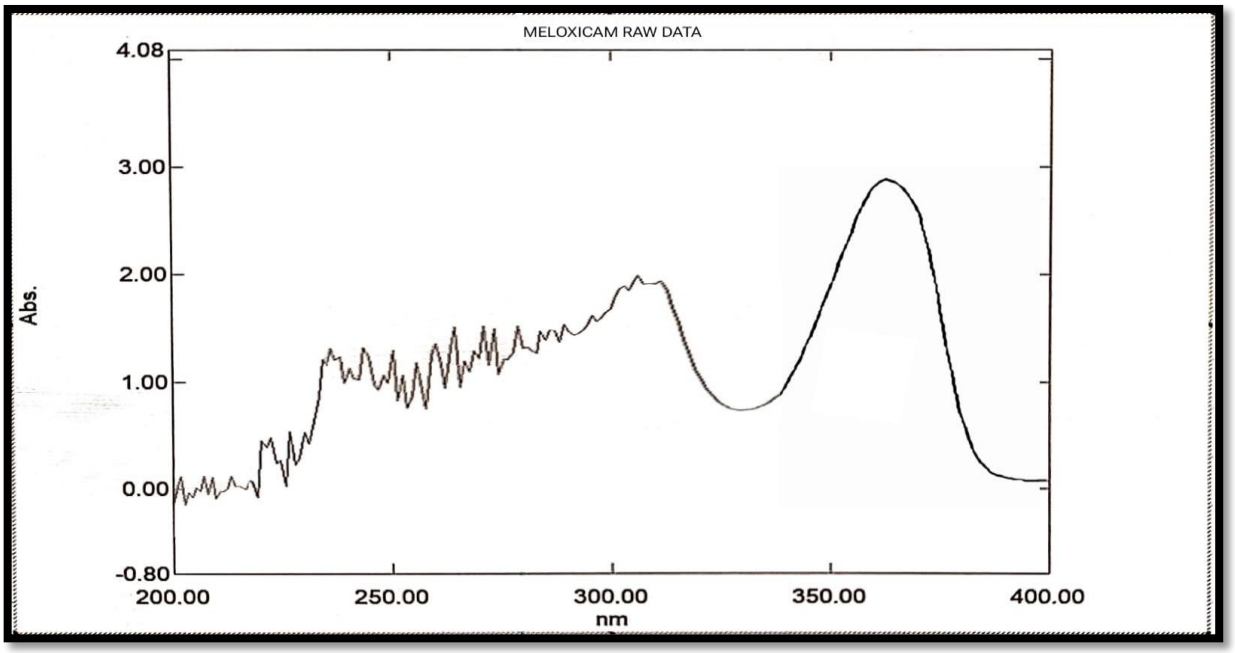

Figure No. 2: λmax of Meloxicam in Dimethylformide.

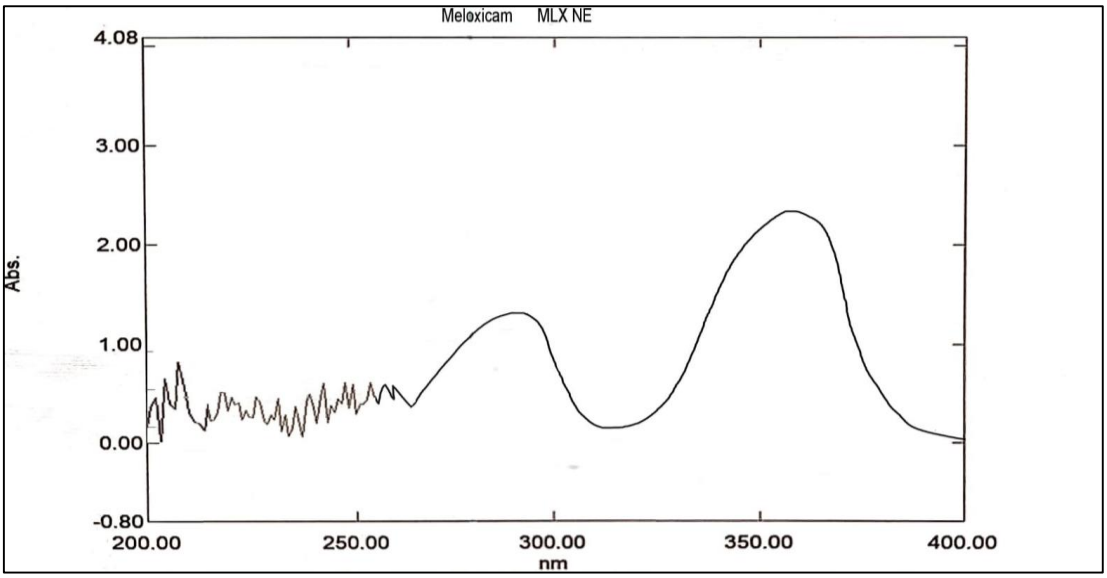

Figure No. 3: λmax of Meloxicam in 0.1 N HCL

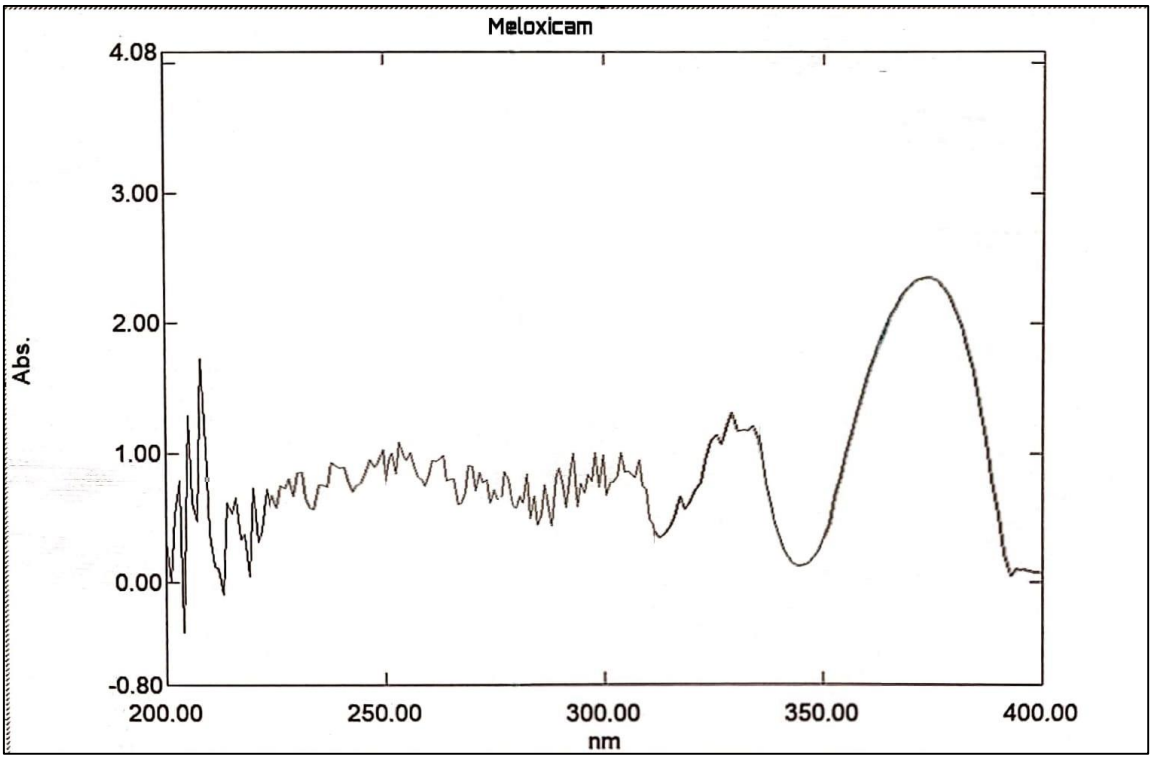

Figure No.4: λ max of Meloxicam in Methanol

Solubility Analysis:

Solubility of meloxicam in different solvents are depicted in table no 17. From the table it is evident that meloxicam is more soluble in phosphate buffer and dimethyl formamide than that of other solvents viz.0.1 N HCl and distilled water.

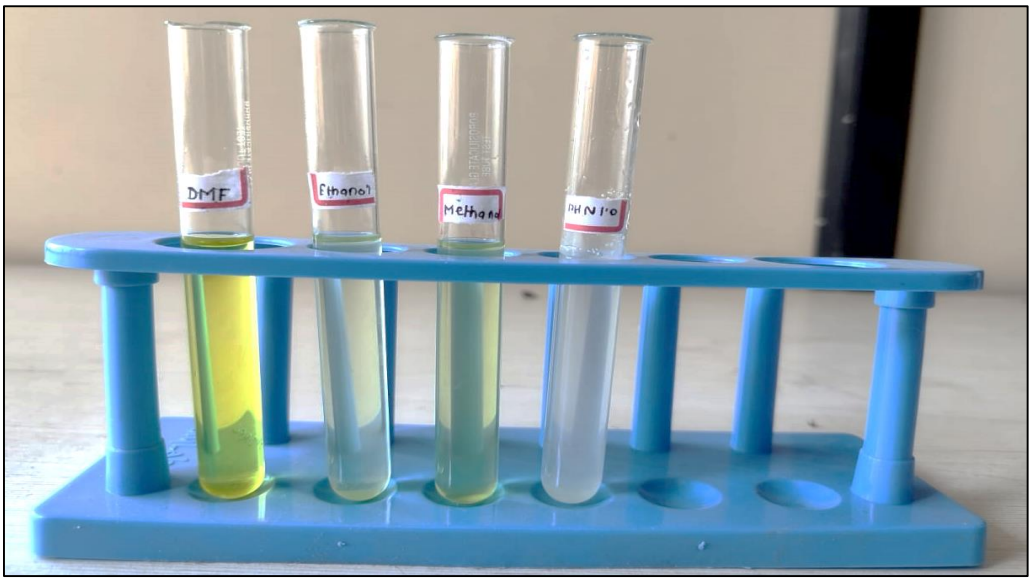

Figure No. 5: Solubility in Various Solution

Table No. 5: Solubility of Meloxicam in different solvents

Sr No	Solvent	Solubility
1	0.1N HCl	Soluble
2	Distilled water	Insoluble
3	Dimethyl formamide	Completely Soluble
4	Methanol	Slightly Soluble
5	Ethanol	Poorly Soluble

Establishment of Calibration curve:

The calibration curve of meloxicam was prepared in methanol at 362 nm. The method estimated the drug concentration in the range of 2-20 micro gram/ML in methanol as it followed the beers lamberts law in the same concentration range.

Table No. 6: Calibration Curve of Methanol in 362 nm

Sr. No.	Concentration	Absorbance
1	0	0
2	2	0.014
3	4	0.027
4	6	0.042
5	8	0.056
6	10	0.073
7	12	0.088
8	14	0.098
9	16	0.114
10	18	0.125
11	20	0.142

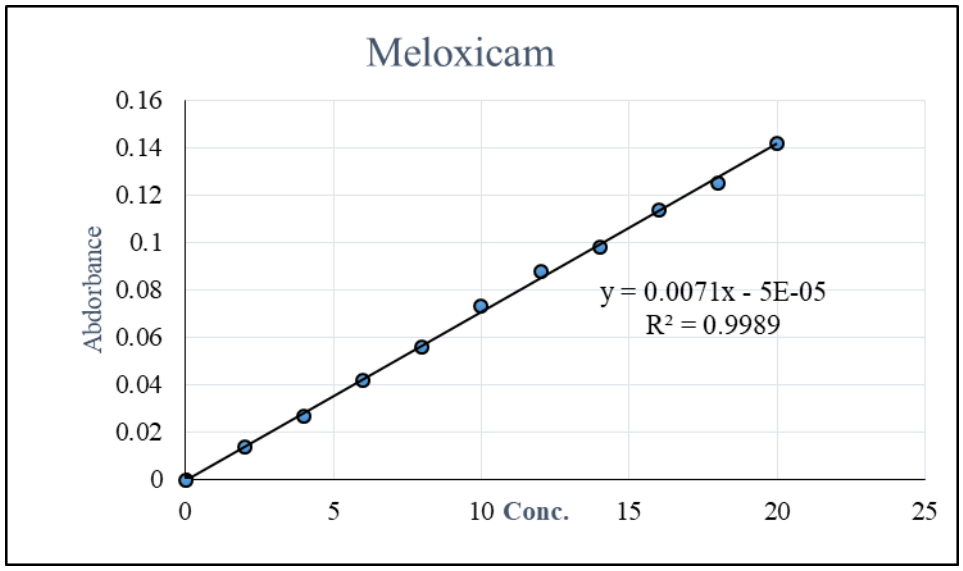

Figure No. 6: Calibration curve of Meloxicam in methanol at λ max 362 nm

XRD of pure Meloxicam:

X ray diffractogram of pure drug meloxicam is shown in Figure no. 18. Presence of sharp peaks in diffractogram indicated the crystalline nature of drug. The nanoparticles are expected to have low crystallinity which should result in lesser peaks with low intensity and blunt peaks are expected with amorphous powders.

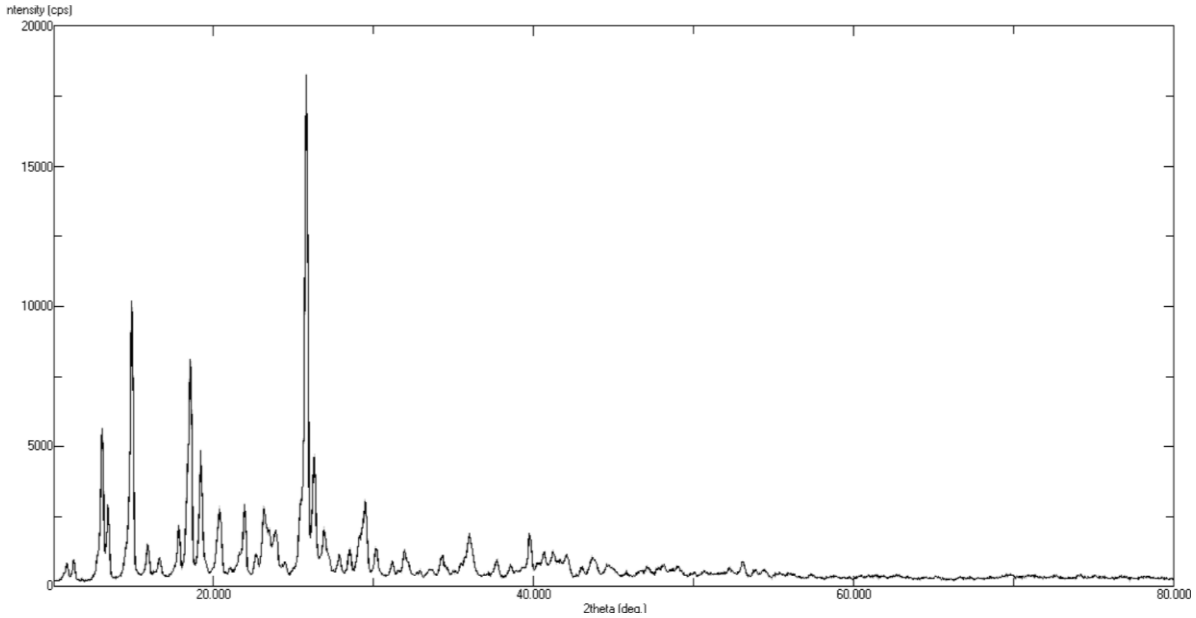

Figure No.7: XRD of MELOXICAM

FTIR Spectral Studies:

FTIR Spectra of pure meloxicam:

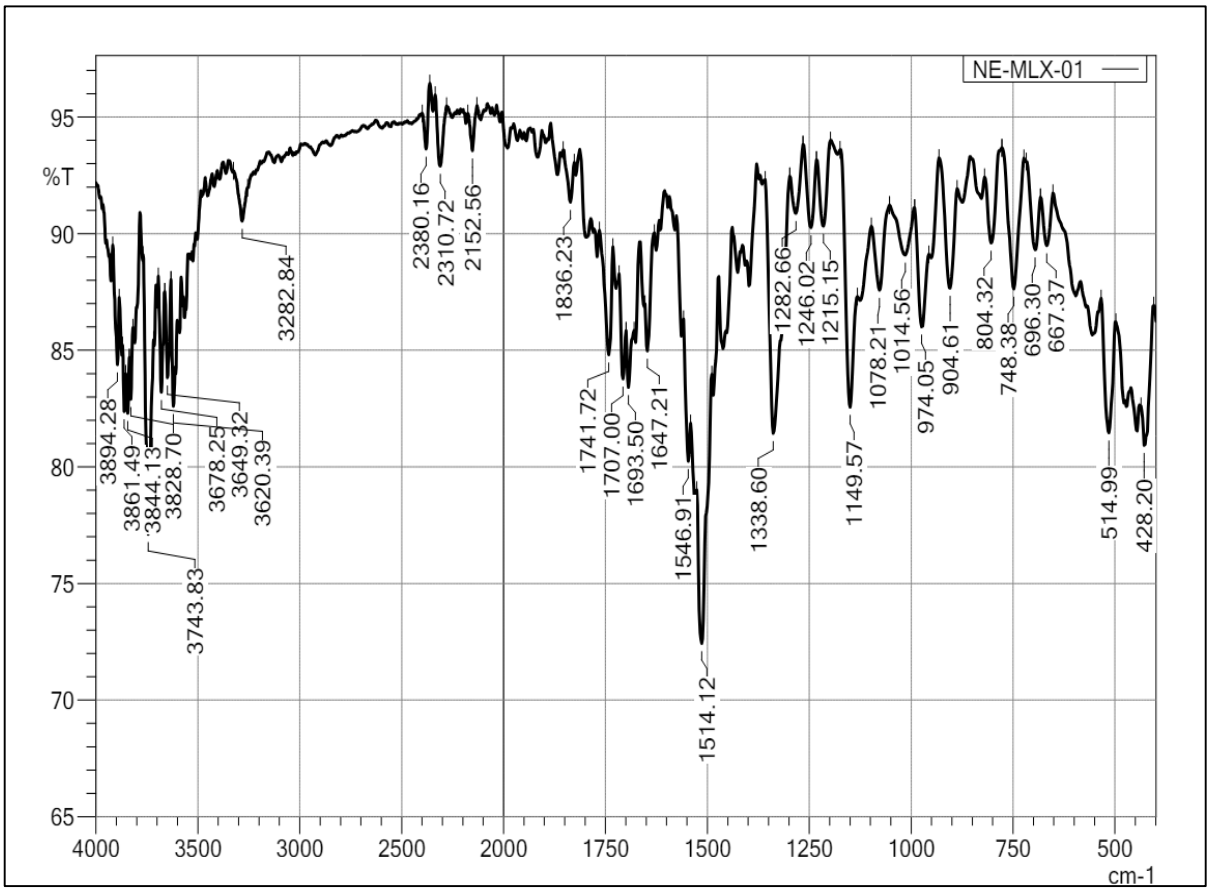

Figure No. 8: FT-IR Of pure Meloxicam

Table No. 7: Characteristics peak of meloxicam

Sr No	Frequency (cm^{-1})	Vibrational Modes
1	3282.84	-NH Stretching
2	1647.21	(C=N)
3	1338.60 & 1149.57 cm-	sulphonyl asymmetric and symmetric stretch

Shows spectrum of the pure meloxicam and it displays characteristics peaks at 3282.84 cm-1 (due to N-H), 1647.21(C=N), 1546.91 cm-1(C=O), 1338.60 cm-1 & 1149.57 cm-1 dur to sulphonyl asymmetric and symmetric stretch.

FTIR Spectra of Drug+Excipient:

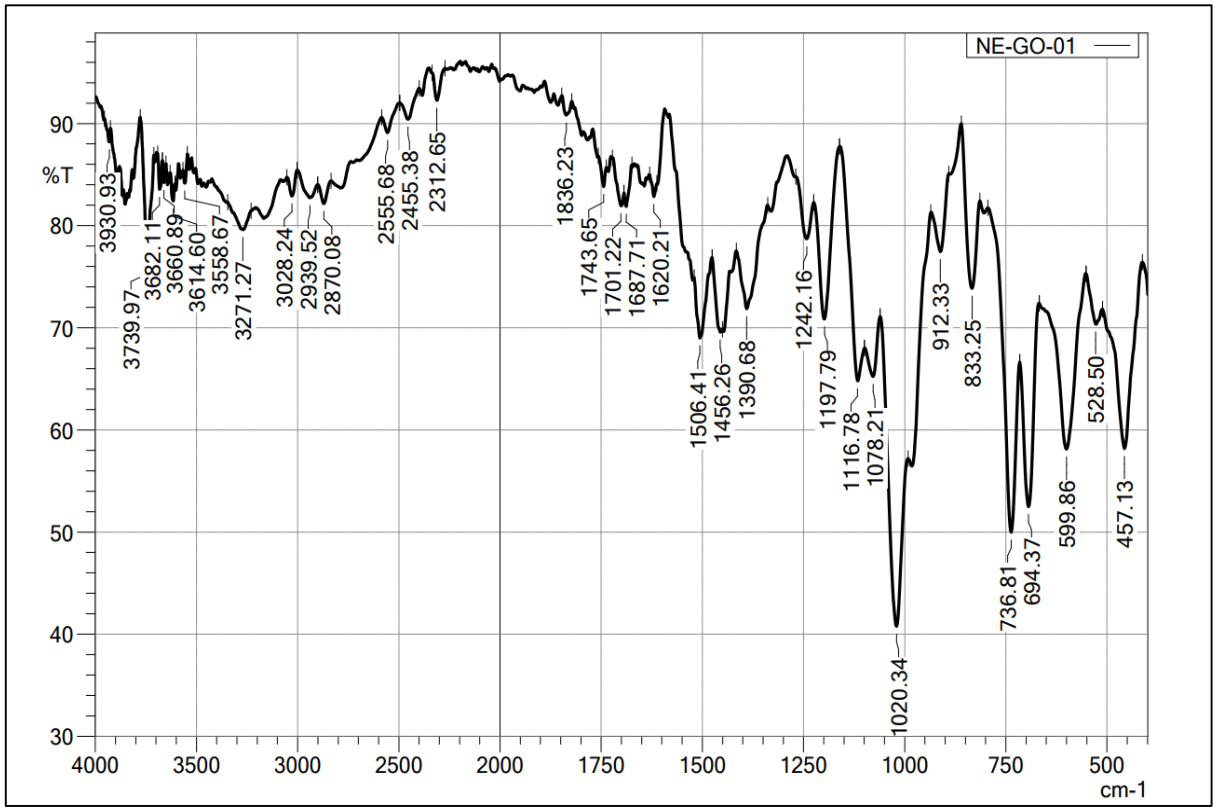

Figure No. 9: FTIR Spectra of Drug+Excipient

FTIR Spectra of Drug+Excipient is given, which show the characteristic band at 3271.27 cm-1 (O-H stretching), 2939.52 cm-1 (CH2 methylene stretch), 1687.71 cm-1 (C=O stretch) 1456.26 cm-1 (C=C aromatic ring stretch), 1390.68 cm-1 (CH3 methyl bond sym), 1020.34 cm-1 (C-OH stretch CH2OH) and 694.37 cm-1 (Phenolic O-H bond).

Table No. 8: Characteristics peak of Drug+Excipient

Sr No	Frequency (cm^{-1})	Vibrational Modes
1	3271.27	O-H stretching
2	2939.52	CH2 methylene stretch
3	1687.71	C=O stretch
4	1456.26	C=C aromatic ring stretch
5	1390.68	CH3 methyl bond sym
6	1020.34	C-OH stretch CH2OH
7	694.37	Phenolic O-H bond

FTIR OF Propylene glycol, Ethanol, Tween 80:

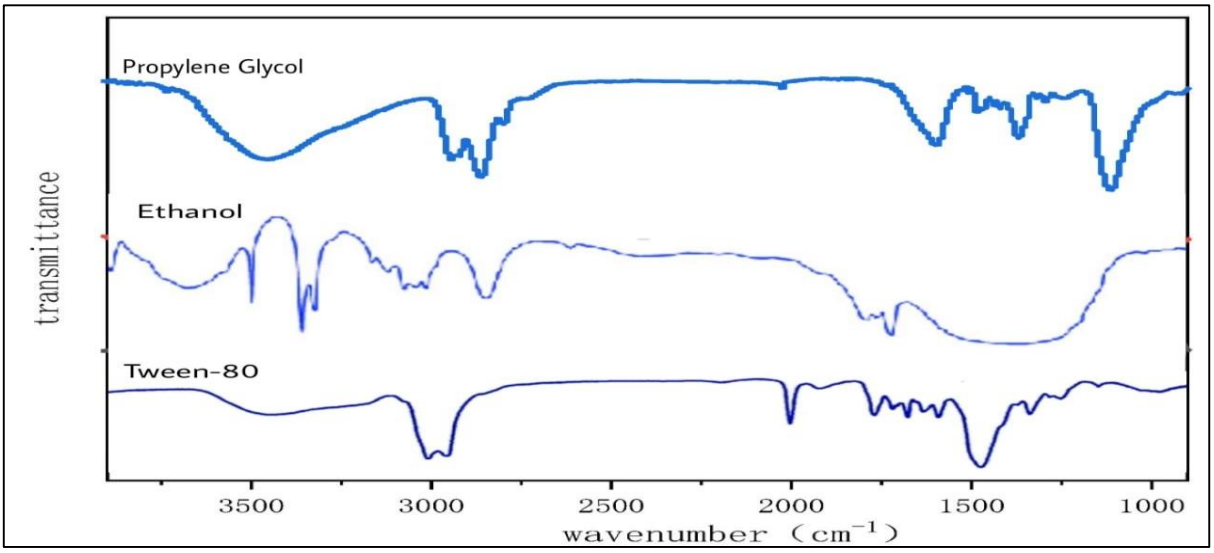

Figure No. 10: FTIR of Excipient (1) Propylene Glycol (2) Ethanol (3) Tween 80

Preparation and Optimization Nanoemulsion of meloxicam

Throughout the process, it's essential to monitor and optimize parameters such as particle size, Zeta potential, Solubility Analysis, and UV-Spectroscopy to ensure the formulation of high-quality topical Nanoemulsion containing Meloxicam. Additionally, adherence to Good Manufacturing Practices (GMP) is crucial to ensure the safety, efficacy, and quality of the final product.

Table No. 9: Formula of preparation of meloxicam

Sr. No.	Ingredient	Plain-NE (ml)	F1	F2	F3	F4	F5
1	Tween 80	6.9	4.5	4.5	6.9	6.9	**3.5**
2	Propylene Glycol	3.75	3.75	2.75	2.75	3.75	**1.55**
3	Ethanol	3.75	3.75	3.75	4.5	3.75	**4.2**
4	Purified water	3.75	3.75	3.75	3.75	2.50	**3.75**
5	Ginger oil	15	17.25	15.25	15	16	**20**
6	Meloxicam	-	2mg	2mg	2mg	2mg	**2 mg**

Based on the provided ingredient quantities for each formulation code (F1 to F5), here's the breakdown of the ingredients in millilitres

Each formulation code represents a different combination of ingredients, varying in the quantities of excipients such as tween 80, Propylene Glycol, Ethanol, Purified Water, ginger oil while keeping the Meloxicam content constant at 35ml. These formulations can be further evaluated for their suitability in the preparation of topical Nanoemulsion of Meloxicam.

CHARACTERIZATION OF TOPICAL NANOEMULSION:

Organoleptic Characterization:

Table 10: Organoleptic Characterization of topical Nanoemulsion

Formulation	Colour	Clarity	Phase Separation
Plain NE	Pale yellow	Homogeneous	No
NE-F1	Pale yellow	Homogeneous	No
NE-F2	Pale yellow	Homogeneous	No
NE-F3	Slightly yellow	Homogeneous	No
NE-F4	Pale yellow	Homogeneous	No
NE-F5	Pale yellow	Homogeneous	No

PARTICLE SIZE OF F5 BATCH:

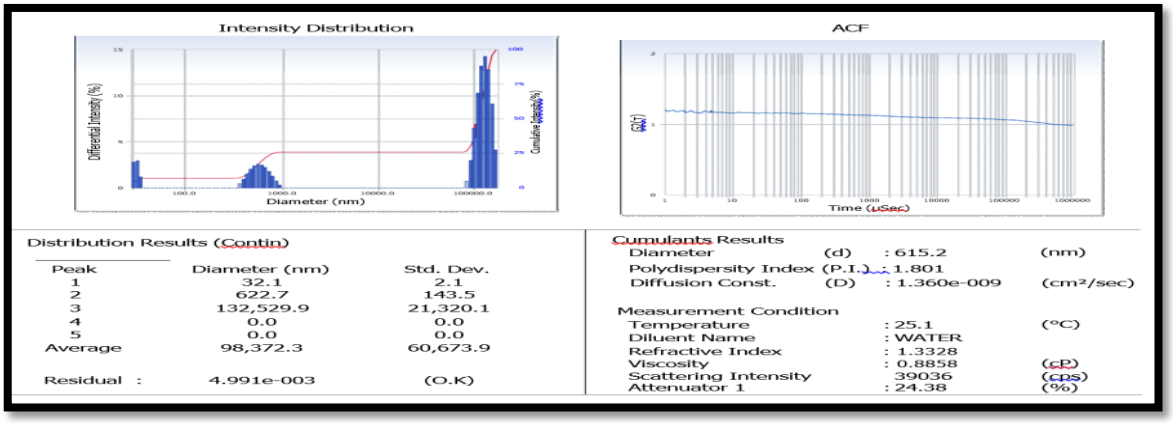

Figure No. 11: Particle size of nanoparticle

Table No. 11: Particle size of drug loaded nanoparticles

SR No.	Batch	Particle size
1	NE-F1	818±0.3 nm
2	NE-F2	697±0.2 nm
3	NE-F3	677±0.3 nm
4	NE-F4	886±0.2 nm
5	NE-F5	615±0.2 nm

The mean particle sizes of MCNPs are shown in Figure no. For the basic formulation (NE-F5) nanoparticle size observed was 615±0.6 nm. With increasing concentration of propylene glycol batch (NE-F1 and NE-F4) particle size was increased significantly from 776±0.3 nm to 910±0.2 nm. Increased meloxicam percent resulted in increased particle size from 779±1.4 nm to 1017±1.5 nm.

ZETA POTENTIAL OF F5 BATCH :

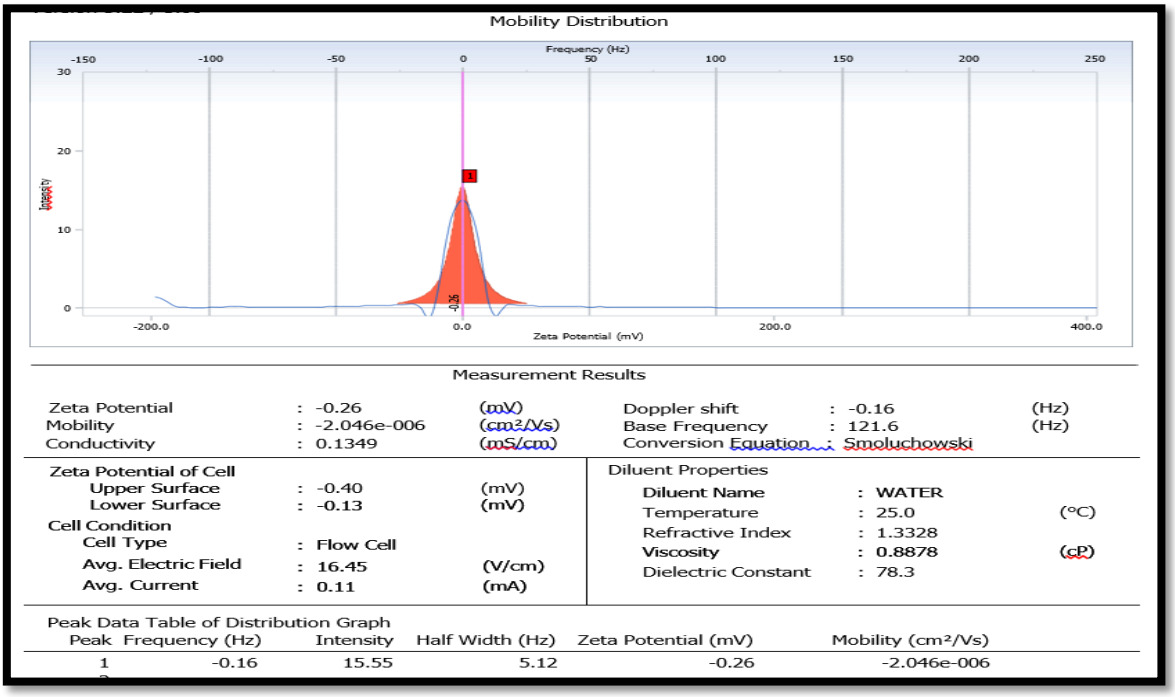

Figure No. 12: Zeta potential of Nanoemulsion

The zeta potential indicate the surface charged on the emulsion and can make predication about its stability The zeta potential of engineered nanoparticles was negative in charged and remained unchanged at all tween 80 concentration. In the first peak the intensity is 15.55, mobility appear -2.046e-006 (cm^2/Vs) the conductivity of nanoparticle is 0.1349 (mS/cm)

Table No. 12: Zeta potential of drug loaded nanoparticles

SR No.	Batch	Zeta potential
1	NE-F1	-22.21±1.12 mV
2	NE-F2	-1.17±0.67 mV
3	NE-F3	-5.55±0.61 mV
4	NE-F4	-17.88±0.9 mV
5	NE-F5	-0.26±0.5 mV

pH :

pH estimation One of the high consequential parameters in the evaluation of Nanoemulaion is the pH. The pH values affect on ionization of the drug i.e. ionized and unionized forms of the drug.

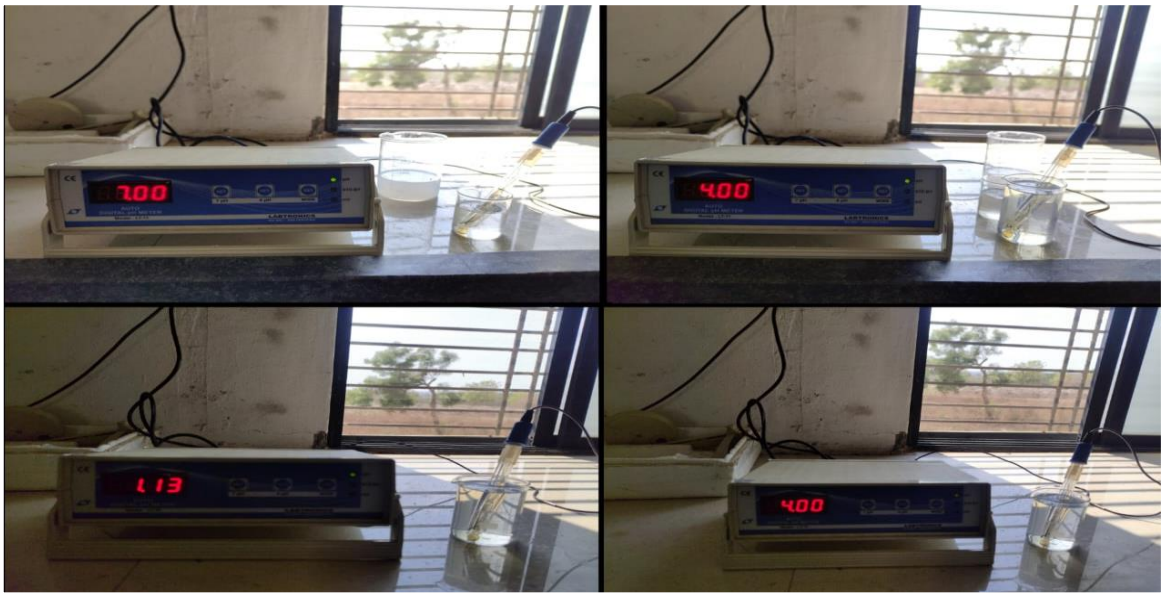

Figure No. 13: Estimation Of pH by Digital pH Meter

Table No. 13: pH of Prepared Nanoemulsion

Formulation	pH
Plain NE	**3-4**
NE-F1	**3-4**
NE-F2	**4-6**
NE-F3	**5**
NE-F4	**4**
NE-F5	**4-6**

The pH of nanoemulsion is very important because of the pH value is affect on the ionization of the drug and the pH of the skin id slightly acidic in nature. The pH of nanoemulsion found between 4-6 range so the nanoemulsion is also slightly acidic

THERMODYNAMIC STABILITY STUDIES:

Centrifugation test:

The formulations were centrifuged for 30 min at 2000 rpm and evaluations were carried out for phase separation, creaming or cracking. Formulations that were found stable were selected and subjected for freeze- thaw stress test and subjected for freeze- thaw stress test. No phase separation occur after the Centrifugation

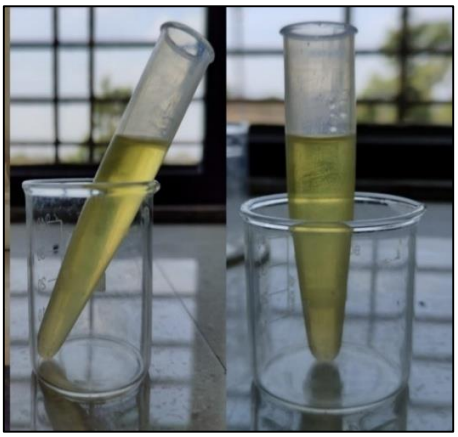

Figure No. 14: Nanoemulsion before Centrifugation

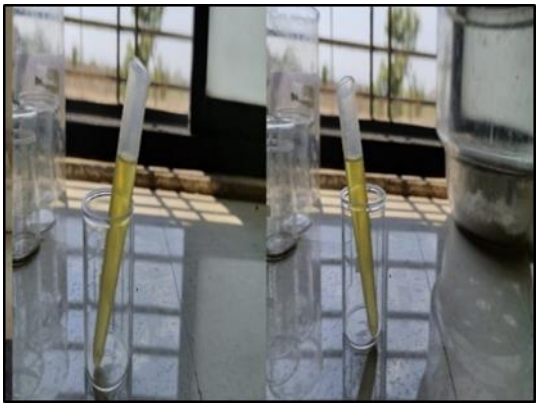

Figure No. 15: Nanoemulsion Centrifugation After

Heating–cooling cycles:

Table 14: Heating-Cooling cycles of nanoemulsion

Sr. No.	Formulation Code	Nanoemulsion at 4^0c	Nanoemulsion At 40^0C	Result
1	**Plain NE**	Stable	Unstable	Satisfactory
2	**NE-F1**	Stable	Viscosity decreased	Satisfactory
3	**NE-F2**	Stable	Viscosity decreased	Satisfactory
4	**NE-F3**	Stable	Viscosity decreased	Satisfactory
5	**NE-F4**	Stable	Viscosity decreased	Satisfactory
6	**NE-F5**	Stable	Stable	Good

FTIR OF FORMULATED NANOEMULSION:

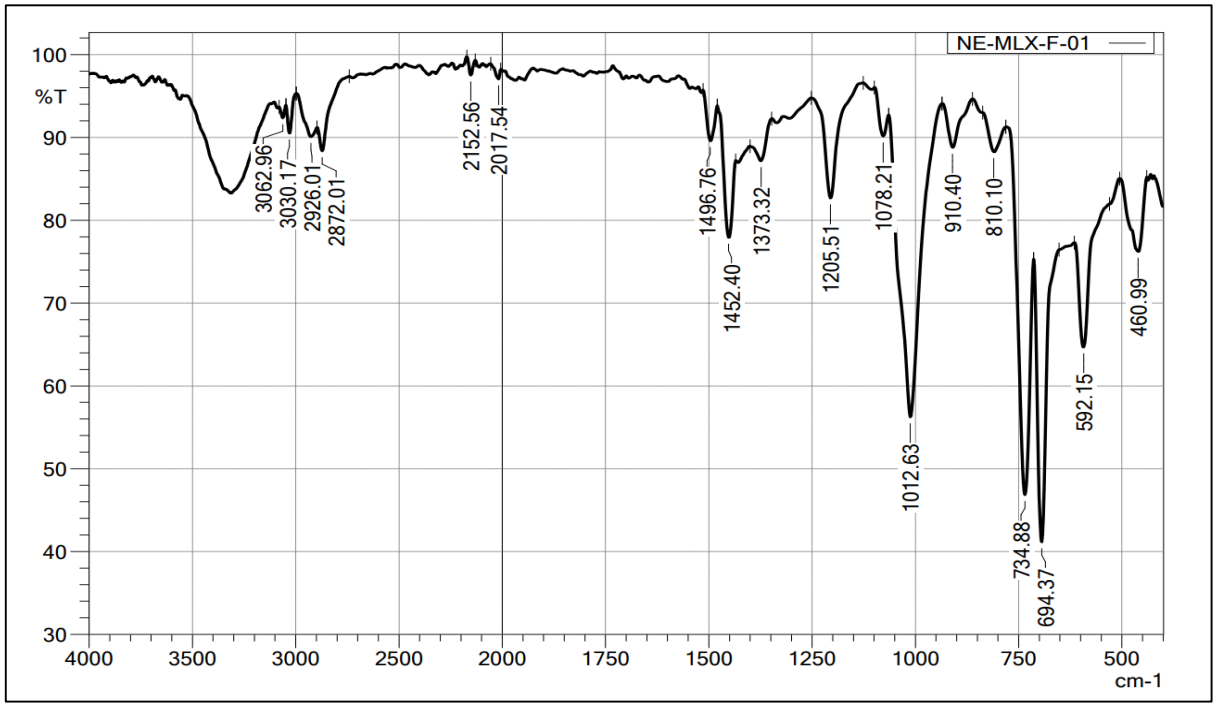

Figure No.16: FTIR OF formulated Nanoemulsion

DSC of Formulated Nanoemulsion:

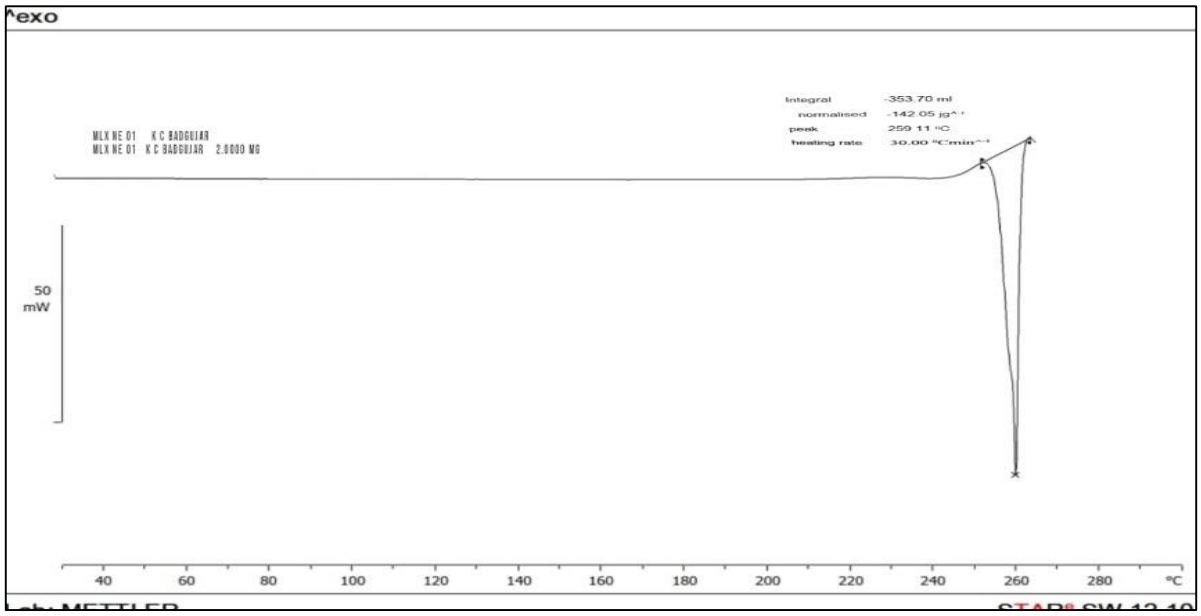

Figure No. 17: DSC of formulated Nanoemulsion

DSC studies of formulated Nanoemulsion were carried out using DSC (Shimadzu, DSC-60, Japan). The DSC thermo gram of the formulated Nanoemulsion showed a sharp endothermic peak at 263 ^{0}C, corresponding to the melting point of the drug.

IN VITRO DISSOLUTION STUDY:

This study was carried out to evaluate the drug release profile of prepared nanoemulsion formulations. The aliquots were analyzed by UV visible spectrophotometer at Amax 355.6 nm. A Franz diffusion cell was used for evaluating the in vitro drug release behavior of the prepared formulations. The receptor medium was filled with freshly prepared phosphate buffer solution (pH 5.5) in a simulation of the skin pH. The temperature of the receptor medium was kept at 32 ± 0.5 °C.

Table No.: 15 In-Vitro Dissolution of Nanoemulsion

Time	PURE MLX	F1	F2	F3	F4	**F5**
0	0	0	0	0	0	**0**
5	3.59	30.97	55.22	38.34	40.94	**39.05**
10	7.04	35.41	57.15	44.45	50	**46.13**
15	8.62	44.72	48.47	50.41	53.84	**51.19**
20	12.77	40.56	53.48	58.03	60.13	**59.64**
25	13.87	54.74	59.14	63.49	64.36	**63.07**
30	15.22	55.37	66.21	69.52	70.16	**67.64**
60	21.35	65.91	70.95	74.96	76.97	**73.62**
90	26.72	71.77	75.97	80.39	82.82	**79.11**
120	30.37	77.58	79.01	84.88	85.8	**88.8**

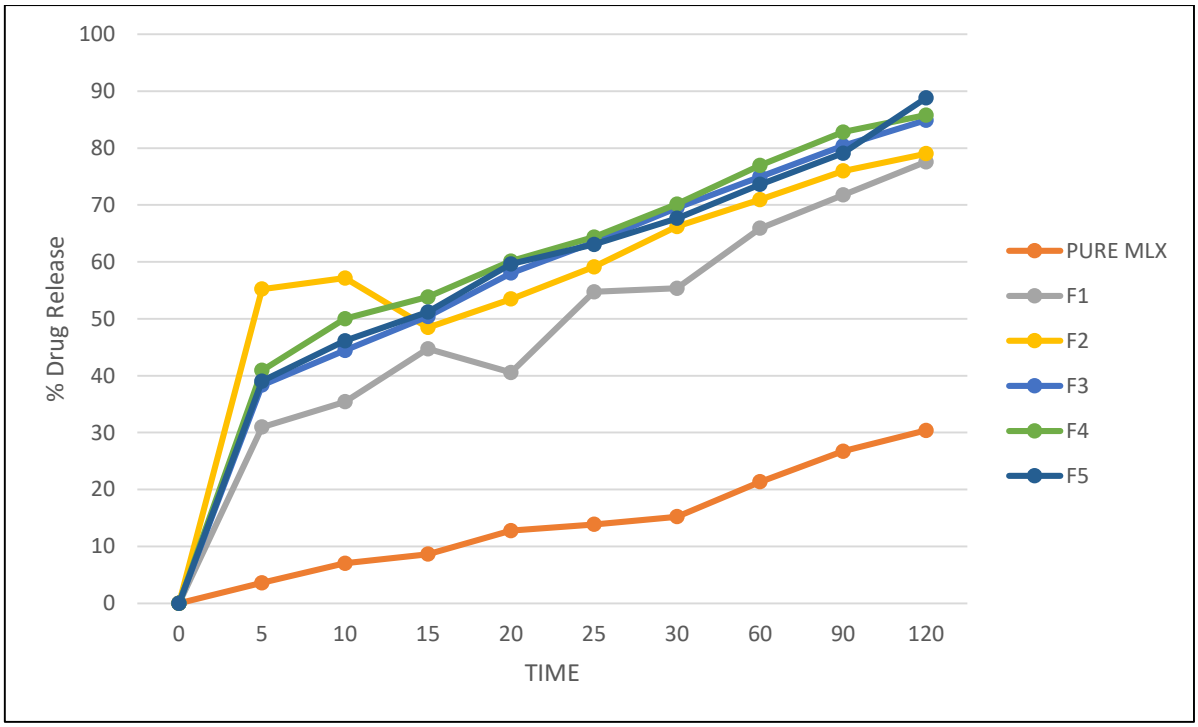

Figure No.18 In-Vitro Dissolution of Nanoemulsion

Formulated Nanoemulsion:

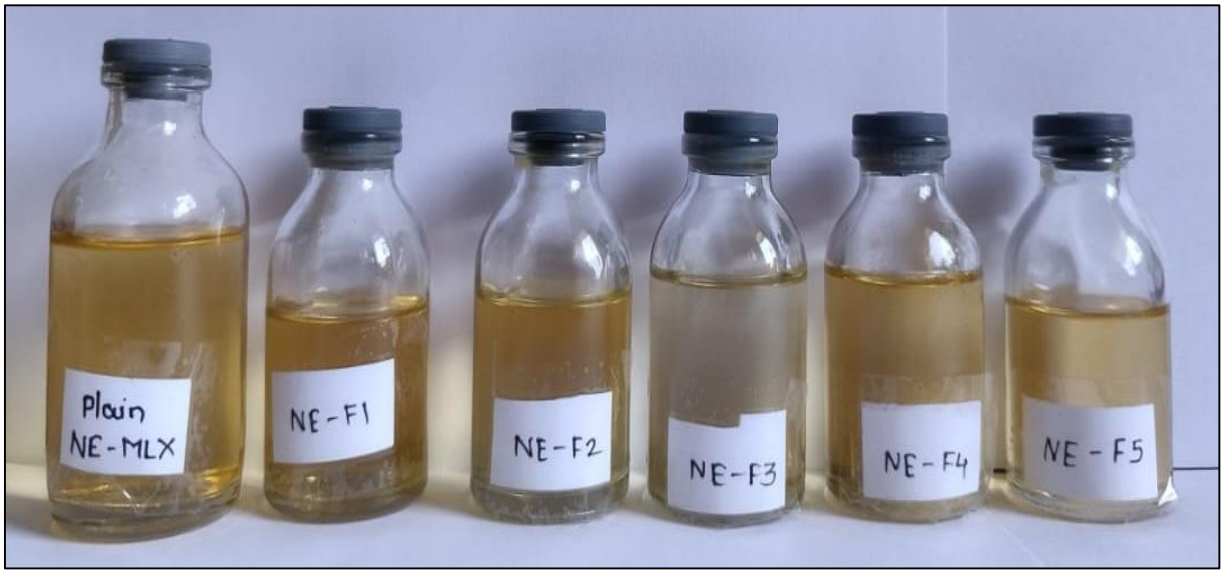

Figure No. 19: Formulated Nanoemulsion

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