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Formulation and Evaluation of Lornoxicam Loaded Nanosuspension Using High Pressure Homogenizer Technique

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Abstract:

Background: Merely exhibiting pH-dependent solubility, lornoxicam is a non-steroid anti-inflammatory drug that is just 18 µg mL−1 soluble in water (pH 7.0). Its numerous disadvantages include low solubility, irritation in the gastrointestinal system, and decreased absorption when taken orally.

Methods: To address the low aqueous solubility, dissolution, and stability issues related to lornoxicam, the primary goal of this research is to prepare a lornoxicam nanosuspension using the High pressure homogenization method with Poloxamer 188, increase its efficiency, and use spray drying techniques to turn the liquid nanosuspension into a solid form.

Results: The physical properties of lornoxicam and the produced nanosuspension were assessed using infrared spectroscopy, powder X-ray diffraction, and differential scanning colorimetry.

Conclusions: Measurements of physicochemical parameters such as solubility and dissolution rate revealed that Lornoxicam Nanosuspension dissolved more quickly than the original drug.

Keywords: Lornoxicam, Nanosuspension, Nanoparticle, Spray drying, Poloxamer etc.

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1. Introduction:

A number of factors, including solubility, stability at ambient temperature, compatibility with solvent and excipient, and photostability, are essential to the effective formulation of pharmaceuticals. To date, lipophilic or poorly water- soluble compounds have accounted for nearly 40% of the novel chemical entities discovered through drug discovery efforts[1]. Drugs with poor solubility and limited bioavailability can be solved using a variety of formulation techniques. Conventional methods such as micronization, fatty solution application, penetration enhancer or cosolvent application, surfactant dispersion method, salt creation, precipitation, etc., have limited effectiveness in Boosting the solubility of weakly soluble pharmaceuticals[2]. The obstacles raised by the previously stated approachescan be overcome via nanotechnology[3]. By using bottom- up methods and top-down methods, the microparticle powder of the drug was transferred into nanoparticles[4]. Surfactants stabilize nanosized drug particles in submicron colloidal dispersions, known as nanosuspensions. Nanosuspensions are made up of weakly water-soluble drugs suspended in dispersion[5]. Drug microparticles/micronized drug powder are transferred to drug nanoparticles using techniques such as Bottom-Up and Top-Down Technology. Submicron colloidal dispersions of medication particles that are nanosized and stabilized by surfactants are called nanosuspensions[6].

Lornoxicam is a non-steroid anti-inflammatory medication that shows pH-dependent solubility, with only 18 μg mL−1 soluble in water (pH 7.0). Effective COX-1 and COX-2 inhibitor, it relieves mild-to-moderate inflammation as well as pain in the short term, especially in rheumatoid arthritis and osteoarthritis. Compared to other oxicams, it has superior abirritation and anti-inflammatory properties. It also has a significant impact on the peripheral and central nervous systems. Nevertheless, it has many drawbacks, including poor solubility, GI tract discomfort, reduced absorption when taken orally[7]. In order to overcome the low aqueous solubility, dissolution and stability issues associated with lornoxicam, The key objective of the study is to prepare nanosuspension of lornoxicam using the HPH method with Poloxamer 188 and to increase its efficiency and to convert liquid nanosuspension into solid form by using spray drying techniques. Differential scanning colorimetry (DSC), powder X-ray diffraction (PXRD), and infrared spectroscopy were used to characterize the physical nature of lornoxicam and prepared nanosuspension

2. Materials and Methods:

2.1 Materials:

Lornoxicam was purchased from Intas Pharmaceuticals located in Pune, India. Additional chemicals were acquired from Molychem Lab in Mumbai; India. The remaining components were all of the analytical or chromatographic grades.

2.2. 3^2 Full Factorial Design:

3^2 factorial designs are a useful technique for examining how various variables affect the quality determining parameters of a formulation. This design was used, in accordance with the design of experiments principle, to examine the impact of two independent influences. Optimizing the various response variables led to the selection of a 32 factorial design with two factors at three levels each. The amounts of the two factors—poloxamer 188 (%) (X1) as well as HPH cycles at 1000bar (X2)—were appropriately coded and changed. The response variables were the particle size nm (Y1) and PDI (Y2). Two elements are considered in this design; Table 1 displays each factor at three levels. Every one of the nine possible combinations that were tested is displayed in Table 2. Throughout the investigation, all other formulation and processing factors were maintained in variation.

Table 1. Variable level of 3^2 factorial designs for lornoxicam nanosuspension

Variable level	-1 (low)	+1 (high)
Poloxamer 188 (%) (X1)	1	3
HPH cycles at 1000bar (X2)	15	25

Table No 2. Formulation of Lornoxicam Nanosuspension using 3^2 factorial designs

Batch Code.	Lornoxicam (mg)	DMSO (ml)	WATER (ml)	(X1) Poloxamer 188 (%)	(X2) HPH cycles at 1000bar
F1	25	10	50	1	15
F2	25	10	50	2	20
F3	25	10	50	3	25
F4	25	10	50	1	15
F5	25	10	50	2	20
F6	25	10	50	3	25
F7	25	10	50	1	15
F8	25	10	50	2	20
F9	25	10	50	3	25

2.3 METHOD:

2.3.1 Preparation of Lornoxicam Nano suspension: To prepare the drug's organic solution, precisely weighed Lornoxicam (25 mg) was dissolved in 10 milliliters of DMSO. To make an aqueous polymer solution, a specified amount of polymer poloxamer 188 (1-3%) was dissolved in 50ml of water. A 0.45 µm filter was used to filter both solutions and an ultrasonic probe sonicator was used to treat the aqueous solution for ten minutes. Addition of organic solvents using a syringe inserted into the polymer containing water so that the needle is facing straight into the polymer. For two hours, the Nanosuspension was continuously stirred at room temperature while organic solvents were allowed to evaporate. In order to obtain the final product, the sonicated Lornoxicam suspensions were further homogenized using a high pressure homogenizer (HPH) that ran at 1000 bar for the necessary number of cycles[8,9].

2.4 Characterization of Liquid state (Nanosuspension):

2.4.1 Particle size and Polydispersity Index analysis:

In order to analyze particle size and Polydispersity index, the produced formulations (1 mL) were diluted with (4 mL) of deionized water then vortexed for approximately 30 seconds. The sample was then processed for particle size analysis while being stored in the Malvern Nano-ZS cuvette (Malvern Instruments, UK)[10,11,12]

2.4.2 Zeta Potential analysis:

Malvern Zeta was used to examine Nanosuspension's zeta potential. After the sample was put in a cuvette with the appropriate dilutions; it was stored in an analyzer to find the Zeta potential[12].

2.4.3 Percentage entrapment efficiency:

Firstly, the nanoparticles generated from the aqueous medium were separated by centrifugation at 10,000 rpm for 20 minutes at room temperature. This allowed researchers to calculate the encapsulation effectiveness of the nanoparticles[14, 15].

2.4.4 Drug release study:

Using a dialysis bag the nanosuspensions' in vitro drug release was accomplished. The medium used for dissolution (phosphate buffer solution, pH 6.8) has a capacity of 900 ml. The medium's temperature was consistently maintained at 37 ± 0.5°C. The device was permitted to operate at 75 rpm. Samples of a 5 ml liquid were taken out at different times. Using a Whatman filter, the materials were purified. Using the same amount of sample each time, the fresh dissolution medium (pH 6.8) was substituted. The drug's λmax (376 nm in a pH 6.8) phosphate buffer solution was used to examine the collected samples[16,17].

2.4.5 Optimization of batch:
The number of batches for the proper optimization of different parameters is provided by the full factorial design with the aid of a design expert. Many designs, such as Fractional Factorial, Central Composite, Plate Burman, and Box Behnkan, are available in Design Expert. The design central composite that was chosen from the list of options above is primarily utilized for variables that have nonlinear responses. The focal point and star design of this design are used in the experimental runs.

2.4.6 Conversion of the Liquid Nanosuspension into solid form:
There are other techniques, such as lyophilization, vacuum drying, spray drying, and heating to evaporation, however we favor spray drying since it uses a smaller amount of energy and time than lyophilization. In contrast to liquid state formulations, solid state formulations exhibit longer term stability. Thus, stable batches from the initial testing were attempted to be powdered using spray drying technology. LOX liquid Nano suspensions were dried into powders using a spray drier. It was 145° C in the inlet air. At 0.6 ml/min, the pump was adjusted. Before spray-drying and adding the aerosol protectant, the 200 ml Lornoxicam Nano suspension was not diluted[18].

2.5 Characterization of Solid state: (Nanoparticles):

2.5.1 Saturation solubility study
We tested the saturation solubility of lornoxicam nanoparticle and the standard drug Lornoxicam in distilled water. Separately, 5 mg of the medication and 5 mg of the nanoparticle equivalent in 5 ml of distilled water were ingested, and they were left to be agitated in an isothermal shaker (37.0 ± 1.0°C) for a 24 h. After being mixed, the samples were placed in test tubes and centrifuged (Remi) for 15 minutes at 10,000 rpm. After filtering and appropriately diluting the samples, spectrophotometric analysis was performed at 376 nm[19].

2.5.2 Fourier Transform Infrared (FTIR) Spectrophotometer study:
Utilizing a Bruker ATR-FTIR spectrometer, ATR-FTIR was carried out to comprehend the relationship between the drug and other excipients. The samples were scanned at 1.0 cm−1 resolution at wavenumbers ranging from 400 to 4000 cm−1[20].

2.5.3 X-Ray Diffraction Studies:
A diffractometer (Pert MPD Model, Phillips, Holland) was used to measure the X-ray powder diffraction of the medication. Using the Cu-target X-ray tube as well as Xe-filled detector, the findings were recorded across a range of 0–40° (2θ). Operating parameters included 40 kV of voltage, 30 mA of current, and a one-minute scanning speed[21,22,23].

2.5.4 Differential Scanning Colorimetric study (DSC):
Thermal behavior of sample was analyzed by using DSC- Shimadzu 60 with TDA trend line software. The temperature rate between 50°C and 300°C at a scanning rate of 20°C/min with nitrogen flow (100 ml/min) [24,25].

2.5.5 Scanning electron microscopy (SEM):
The surface morphology of nanoparticles was examined using scanning electron microscopy (JEOL Model JSM-6390LV). Using double-sided sticky tape, the nanoparticles were directly attached on the SEM stub. They were then coated with platinum as well as scanned using a concentrated electron beam in a high vacuum chamber. The image was created by detecting secondary electrons that were released from the materials[26,27].

2.5.6 Stability Study of Nanoparticles:
The loaded NPs of Lornoxicam Poloxamer 188 were kept for a month at room temperature and between 2- 8^{o} C. UV Spectroscopy was used as an analytical technique to determine the percentage drugs content of the formulations after each week[28,29].

3. Results and Discussion:
3.1 Particle Size and Size distribution analysis:
In addition to having a PDI of less than 0.5, a consistent distribution of particle sizes is essential for the stability of the nanosuspension. The system's stability may be significantly impacted by particle aggregation caused by a wide size distribution. The F3 batch of nanosuspension demonstrated a better effect on particle size reduction; table 3 shows mean particle size and PDI values of 452.7 nm and 0.512 nm, respectively. This outcome unequivocally demonstrates the value of the HPH approach for nanosizing. This indicates that every nanoparticle that has formed is

uniformly sized or monodispersed. Since nanoparticles have diameters in the nanometer range, we should anticipate better drug release than with pure drug.

Table 3.Particle size and Polydispersity Index of formulation

Sr. No.	Batch No.	Particle size (nm)	PDI
1	F1	525	0.726
2	F2	473	0.612
3	**F3**	**452**	**0.512**
4	F4	590	0.700
5	F5	470	0.680
6	F6	536	0.672
7	F7	657	0.711
8	F8	531	0.691
9	F9	643	0.654

3.2. Zeta potential :

The total charge that a particle accumulates in a specific medium is known as its zeta potential.It is employed in the prediction of interactions between particles. In general, stable nanoparticles are those with zeta potentials between ≤−30 and ≥+30 mV. Batch F3 zeta potential was -11.2, as shown in Fig. The stable colloidal suspension was shown by the nanoparticles' zeta potential values falling within the specified range.

3.3. Entrapment efficiency:

The process of initially removing the nanoparticles that had generated from the aqueous medium involved centrifugation at 10,000 rpm for 20 minutes at room temperature in order to measure the encapsulation effectiveness of the particles.

Table 4. Entrapment efficiency of formulation

Sr. No.	Batch No.	% Entrapment Efficiency
1	F1	90±0.018
2	F2	91±0.019
3	**F3**	**93±0.012**
4	F4	91±0.031
5	F5	92±0.015
6	F6	92±0.021
7	F7	89±0.038
8	F8	90±0.024
9	F9	91±0.021

Mean ± S.D., n=3

3.4. In vitro Dissolution study:

Display the dissolution profile of both batches and pure Lornoxicam in Figure.1.Dissolution profile of pure Lornoxicam reveals 32% drug release for duration of 60 minutes. Polymers (poloxamer188) caused Lornoxicam to dissolve more readily. The increase in surface area caused by the reduction of particle size may be the reason for the improvement in nanoparticle dissolution. Furthermore, it was evident that an increase in the molar ratios of polymers in the produced nanosuspension improved the dissolution of Lornoxicam. According to the dissolving profiles of the nanosuspension batches, batch F-3 required 30 minutes to reach 90% drug release. This indicates that Poloxamer 188 can dissolve Lornoxicam quickly. It is possible that theincreased surface area and saturation solubility of the nanoparticles contributed to the Nano suspension's significantly higher dissolving rate when compared to the plane medication.

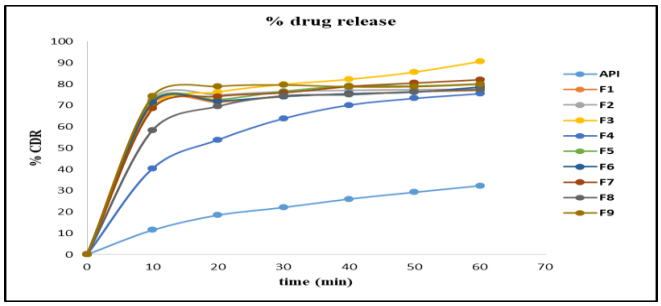

Figure.1 % cumulative drug release of nanosuspension Batches and pure API

3.6. Optimization of batch using 3^2 factorial designs:

Mathematical modeling and statistical analysis using ANOVA:
Mathematical model was developed to understand effect of concentration of Poloxamer 188 and HPH cycles at 1000 bar on the responses.

Counter plot:
To investigate the interaction effect of the factor on the replies, two-dimensional counter plots are highly helpful. Plots of this kind are helpful when examining the simultaneous effects of two factors on a response.

3.6.1. Counter plot of Particle size (Y1) with variables X1 and X2:

The counterplot revealed it. Figure No.2. Demonstrates how increasing the concentration of Poloxamer 188 up to a specific point led to a decrease in the particle size of Lornoxicam NPs and a rise in particle size after that. The results indicated a decrease in the interfacial tension between the anti-solvent and aqueous phase, which could potentially regulate drug particle aggregation by facilitating particle partition and leading to smaller particle sizes. Similarly, a high surfactant concentration can increase drug solubility in the external phase and potentially increase drug partitioning from the internal phase to the internal phase. With an increase in HPH cycles at 1000 bar, the particle size decreases.

3.6.2. Counter plot of PDI (Y2) with variables X1 and X2:

The counter plot in Figure 8.13 revealed that an increase in Poloxamer 188 concentration resulted in a decrease in the PDI of Lornoxicam NPs. It revealed a decrease in the interfacial tension between the anti-solvent and the aqueous phase, suggesting that this could regulate drug particle aggregation by facilitating particle partition and lowering PDI. In the same manner, a high surfactant concentration makes the drug more soluble in the external phase and may also accelerate the drug's partitioning from the internal phase into the internal phase. The PDI rises as the concentration of surfactant decreases. The drug's PDI decreases when a high surfactant concentration is present. This rise in PDI may result in larger particles with higher PDI and less homogeneity during the initial phase of suspension.

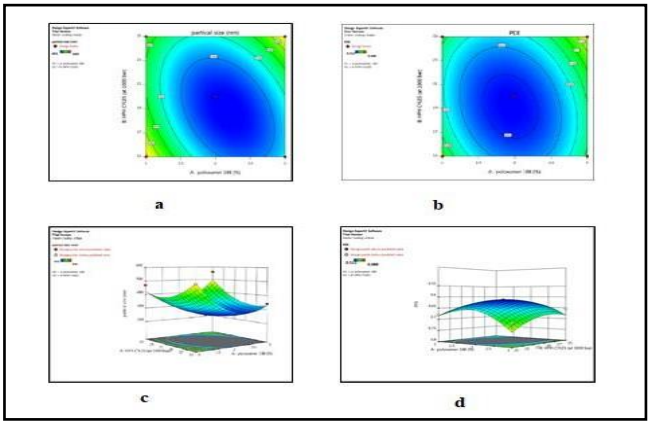

Figure 2. Counter plot and 3D response surface plots showing the effects of independent factors on (a) Particle size, b) PDI, c) Particle size, d) PDI

3.7. Saturation solubility study:

If the nanoparticles' particle size is lowered below a certain threshold, their saturation solubility will rise. As a result, nanonization may boost the produced nanoparticles' saturation solubility. As per the solubility study results, pure LOR has an extremely low solubility of 0.01827 µg/mL in water. The Lornoxicam nanoparticles' water solubility was significantly increased in this investigation. The Lornoxicam nanoparticle Batch F3 (0.9069 µg/mL) had a saturation solubility that was nine times higher than that of the drug in its pure form. The much higher saturation solubility was caused by the Lornoxicam particle size reduction to nanoscale, which also increased surface area and improved hydrophilicity.

3.8. Fourier Transform Infrared study:

Pure lornoxicam's FTIR spectrum shows a distinctive peak at 3067.54 cm-1, which is caused by the NH group's stretching vibration. The first sharp peak found at 1621 cm-1 is the the primary amide's C=O stretching vibration. The N-H group's bending vibrations in the secondary amide are shown by additional peaks that were found at 1591 cm-1 and 1530 cm-1. Peaks reported at 1379 and 1143 cm-1 are caused by O=S=O stretching vibrations. The aromatic ring bending of C-H is represented by peaks obtained at 802 cm-1, while the bending vibration of C-C1 is represented by peaks obtained at 787 cm-1. A drug's purity can be determined by looking for all of these groups because they are identical to the real drug structure. Peak intensities and wave numbers in the FTIR spectra of the pure drug and Lornoxicam nanosuspension (nanoparticles) after spray drying does not significantly differ, suggesting that neither the spray drying nor the nanosuspension processes affect the stability of the drug or the interaction between stabilizers (Fig. 3). Therefore, in this investigation, no effects of the chosen polymers as well as nano with dried method were seen.

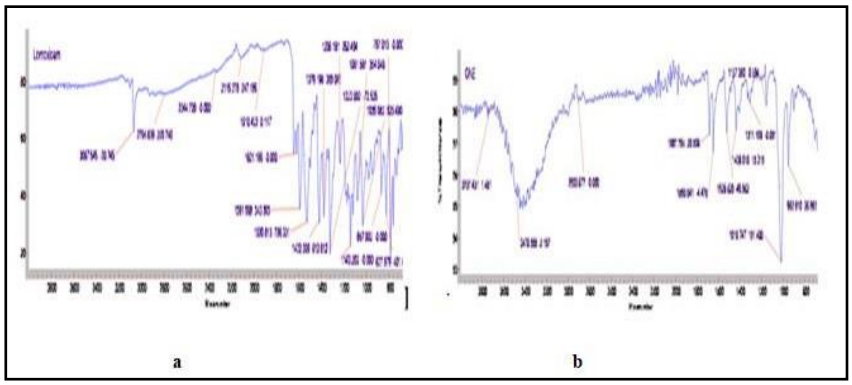

Figure. 3 FTIR of A) Lornoxicam, B) F3 Batch

3.9. X-Ray diffraction analysis:

The crystalline character of Lornoxicam is indicated by the crystalline peaks 2θ values from 10 to 23° that the pure Lornoxicam exhibited. However, following the synthesis of lornoxicam nanoparticles by spray drying procedure, as seen in the XRD pattern of batch F3, the degree of crystallinity, which is represented as intensity in the XRD diagram, was dramatically lowered. The generated nanoparticle pattern showed an amorphous substance instead of the characteristic crystalline peaks, indicating a significant drop in the crystallinity of Lornoxicam. Consequently, it is reasonable to anticipate that throughout storage, the spray-dried nanoparticles will remain physico-chemically stable. Better physicochemical qualities, such as improved solubility and dissolution, can also be reasonably ascribed to the reduction of particle size rather than changes in the crystalline state.

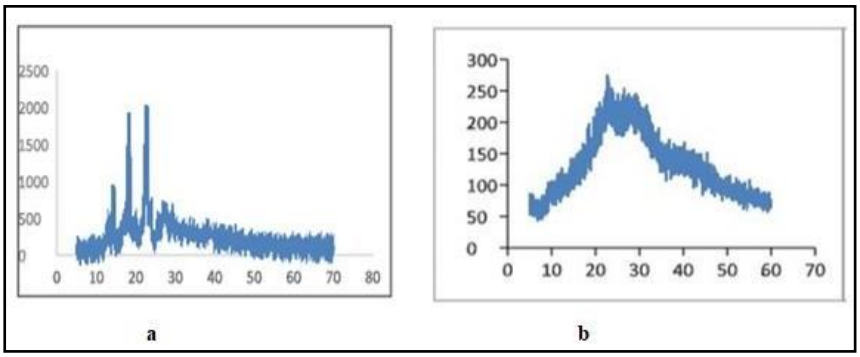

Figure. 4 XRD patterns of A) Lornoxicam, B) F3 Batch

3.10. Differential Scanning Calorimetry (DSC):

Figures 5 display the DSC thermograms of the pure drug as well as the nanoparticles made with polymer (Poloxamer 188). DSC curves for lornoxicam and lornoxicam nanoparticles show a single, strong endothermic peak that corresponds to the melting points of batch F3 lornoxicam nanoparticles at 231.67°C and lornoxicam at 228.36°C. When comparing the nanoparticles with pure drug, there was no discernible difference in the melting peak. Following the precipitation process, there may be a little shift in melting point that is related to the particle size being reduced to the nanoscale range.

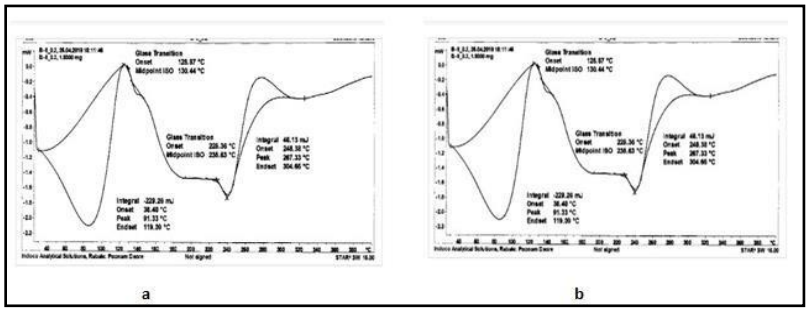

Fig. 5. DSC thermo gram of a) Lornoxicam, b) F3 Batch

3.11 Scanning electron microscopy:

The SEM pictures may be shown in Figures 6. The pure medication particles were visible as needle-shaped microcrystals. In contrast, the LOX nanoparticles produced by the HPH technique were dried by In the presence of a poloxamer combination, the spray-dried particles had a narrow particle size distribution and were spherical. It was evident that polymers were adsorbed onto the surface of the drug particle, preventing particle development and stabilizing the nanoparticles. By employing the nanosuspension spray-dried process, it is anticipated that the production of spherical particles will enhance the solubility of dried nanoparticles of Lox.

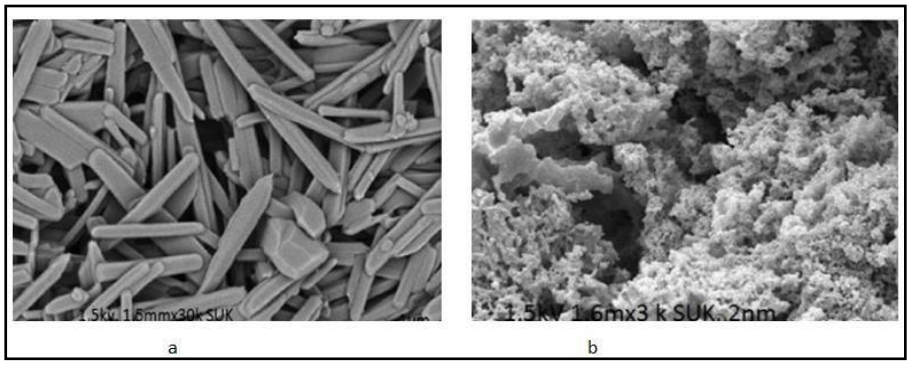

Fig. 6. SEM of a) Lornoxicam, b) F3 Batch

3.12. Stability Study of Nanoparticles:

Samples retained for stability studies had their drug content assessed at prearranged intervals.

For 30 days, the Lornoxicam-Poloxamer 188 loaded NPs were kept at room temperature and between 2 and 8 °C. The stability analysis of Lornoxicam Poloxamer 188 loaded NPs for 30 days is displayed in Table No. 5. Since the drug content has not changed significantly, we can conclude that the formulation is stable

Table 5. % Drug content of batches after stability study

% Drug content	
Period	**F3 Batch**
0 month	88.97±0.32
1 month	88.47±0.14

Mean ± S.D., n=3

4. Conclusions:

The current work shows that impediments to lornoxicam's systemic circulation, such as dissolution rate, water solubility, and stability, may be eliminated by forming nanosuspensions. When compared to the original molecule, the Nano suspension made with HPH techniques showed much greater solubility and dissolution rates. The study demonstrated how simple it is to manufacture nanosuspension utilizing HPH techniques. XRD, DSC, and IR examinations were used to validate the development of Nano suspensions. It was found that nanosuspension remained stable for a month.

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Conflicts of Interest

"The authors declare no conflict of interest."

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