FORMULATION AND EVALUATION OF NANOPARTICLE BASED DRUG DELIVERY SYSTEM FOR ENHANCED BIOAVAILABILITY WITH THE HELP OF LORNOXICAM

[1]Mr. Anant Guthe; [2]Ms. Mirabai R. Deokar ; [3]Dr. Pravin Uttekar

Dnyan, Kala, Krida, & Krishi Pratishthan's, Late Laxmibai Phadtare College of Pharmacy, At Post: Kalamb Walchandnagar, Tal.Indapur, Dist. Pune - 413114

Abstract:

Background: Lornoxicam is a potent non-steroidal anti-inflammatory drug (NSAID) widely used for the management of pain and inflammation. However, its poor aqueous solubility and limited oral bioavailability restrict its therapeutic effectiveness. Nanoparticle-based drug delivery systems have emerged as a promising strategy to overcome these limitations by enhancing drug solubility, stability, and controlled release. Objective: The present study aimed to formulate and evaluate Lornoxicam-loaded nanoparticles to enhance the drug's bioavailability and therapeutic performance. Methods: Lornoxicam-loaded nanoparticles were prepared using the solvent evaporation method and optimized through a Box–Behnken experimental design. The prepared formulations were evaluated for particle size, polydispersity index (PDI), zeta potential, drug content, entrapment efficiency, percentage yield, and in vitro drug release. The optimized formulation was further characterized using Fourier Transform Infrared Spectroscopy (FTIR), X-ray Diffraction (XRD), and stability studies. Drug release kinetics were analyzed using Zero-order, First-order, and Higuchi models. Results: The optimized formulation (F10) exhibited a particle size of 124.6 nm, PDI of 0.142, and zeta potential of −29.6 mV, indicating excellent nanoscale characteristics and colloidal stability. The formulation showed 94.26% drug content, 86.23% entrapment efficiency, and 95.85% percentage yield. In vitro drug release reached 94.88% within 300 minutes, demonstrating sustained drug release. Release kinetic analysis revealed that the formulation best followed the Higuchi model (R^2 = 0.9902), indicating diffusion-controlled drug release. FTIR analysis confirmed the compatibility of Lornoxicam with formulation excipients, while XRD studies demonstrated the conversion of the drug into a predominantly amorphous form. Stability studies over three months indicated minimal changes in physicochemical properties, confirming good formulation stability. Conclusion: The developed Lornoxicam-loaded nanoparticle formulation successfully improved drug release characteristics, stability, and physicochemical properties. The optimized nanoparticle system represents a promising approach for enhancing the oral bioavailability and therapeutic efficacy of poorly water-soluble drugs such as Lornoxicam.

Keywords: Nanoparticles, Drug Delivery System, Bioavailability, Nanotechnology, Controlled Drug Release, Polymeric Nanoparticles, Drug Entrapment, Pharmaceutical Formulation

1. INTRODUCTION:

Nanotechnology has emerged as a promising approach to overcome the limitations associated with conventional drug delivery systems, particularly for poorly water-soluble drugs and herbal bioactive compounds. Nanoparticle-based drug delivery systems have attracted significant attention due to their ability to improve drug solubility, stability, permeability, controlled release, and therapeutic efficacy. The present study was undertaken to formulate and evaluate a nanoparticle-based drug delivery system aimed at enhancing the bioavailability of the selected drug/extract using a biodegradable polymeric carrier. Nanoparticles were prepared by an appropriate formulation technique and optimized using a statistical experimental design to achieve desirable physicochemical characteristics. The prepared formulations were evaluated for particle size, polydispersity index (PDI), zeta potential, entrapment efficiency, drug content, and in vitro drug release. Compatibility between the drug and excipients was assessed using Fourier Transform Infrared Spectroscopy (FTIR), while the physical state of the optimized formulation was characterized by X-ray Diffraction (XRD).

The optimized nanoparticle formulation exhibited a nanoscale particle size with uniform size distribution, adequate surface charge, high drug entrapment efficiency, and satisfactory physicochemical stability. The in vitro drug release study demonstrated a sustained release profile, suggesting prolonged therapeutic action. Furthermore, biological evaluation indicated enhanced pharmacological activity compared with the conventional formulation, which may be attributed to improved absorption and bioavailability offered by the nanoparticle system. The findings of this study demonstrate that nanoparticle-based drug delivery systems provide an effective strategy for improving the therapeutic performance of drugs by enhancing solubility, protecting active constituents from degradation, and facilitating controlled drug release. The optimized formulation showed promising characteristics suitable for further preclinical and clinical investigations. Overall, nanoparticle-based drug delivery represents a novel and efficient platform for improving drug bioavailability, minimizing dosing frequency, and enhancing patient compliance, making it a valuable approach in the development of advanced pharmaceutical formulations.

2. MATERIALS AND METHODS:

2.1. Materials: Lornoxicam was obtained as a gift sample from Solanki Enterprises, Pune. Eudragit RL100, Compritol® ATO 888, polyvinyl alcohol (PVA), methanol, ethanol,

DMSO, phosphate buffer, dialysis membrane, and other analytical-grade chemicals were used throughout the study.

2.2. Preformulation Studies: Preformulation studies included drug identification, melting point determination, solubility analysis, wavelength (λmax) determination, and preparation of calibration curves in different solvents. Drug–excipient compatibility was evaluated by Fourier Transform Infrared (FTIR) spectroscopy, while X-ray diffraction (XRD) was performed to determine the crystalline nature of the drug.

2.3. Preparation of Lornoxicam-Loaded Nanoparticles: Lornoxicam-loaded nanoparticles were prepared by the nanoprecipitation method. Eudragit RL100, Compritol® ATO 888, and Lornoxicam were dissolved in acetone, followed by the dropwise addition of an aqueous PVA solution under continuous stirring. The organic solvent was removed using a rotary evaporator, and the nanoparticle suspension was centrifuged, washed, dried, and stored in a desiccator until further use.

2.4. Experimental Design: The formulation was optimized using a Box–Behnken Design (BBD) under a Quality by Design (QbD) approach. Lipid concentration, polymer concentration, and stabilizer concentration were selected as independent variables, while particle size, zeta potential, and drug content were evaluated as dependent responses. A total of 13 formulations were prepared and analyzed.

2.5. Evaluation of Nanoparticles: The prepared nanoparticles were characterized for particle size, polydispersity index (PDI), zeta potential, drug content, entrapment efficiency, and percentage yield using standard analytical techniques. Drug content and entrapment efficiency were determined by UV spectrophotometry at 375 nm.

2.6. In Vitro Drug Release and Characterization: The in vitro drug release study was performed using the dialysis bag diffusion method in phosphate buffer (pH 6.8). Release data were fitted to kinetic models, including zero-order, first-order, and Higuchi models. The optimized formulation was further characterized using FTIR and XRD to assess drug–excipient compatibility and crystallinity.

2.7. Stability Study: The optimized formulation was subjected to stability testing according to ICH guidelines at 30 ± 2°C/65 ± 5% RH and 40 ± 2°C/75 ± 5% RH for three months. Periodic evaluation of particle size, zeta potential, and drug content was performed to assess formulation stability.

3. RESULTS AND DISCUSSION

3.1 Preformulation Studies of Lornoxicam

Preformulation studies were carried out to evaluate the physicochemical characteristics of Lornoxicam prior to the development of the nanoparticle formulation. These studies are essential for understanding the drug's properties and selecting appropriate formulation strategies to enhance its therapeutic performance.

The physical examination of Lornoxicam revealed that the drug was obtained as a yellow crystalline powder with a characteristic appearance, which was consistent with the standard description of the pure active pharmaceutical ingredient. The identity and purity of the drug were further confirmed by melting point determination. The observed melting point was 218.6°C, which closely matched the reported melting point range of 219–222°C. The slight variation may be attributed to instrumental or experimental conditions and remained within acceptable limits. These findings confirmed the crystalline nature and purity of the drug, indicating its suitability for formulation development.

The UV spectrophotometric analysis demonstrated that Lornoxicam exhibited a maximum absorbance (λmax) at 375 nm, which was in close agreement with the reported value of 376 nm. This result confirmed the identity of the drug and validated the selected wavelength for quantitative estimation during subsequent analytical studies. The close agreement between the observed and reported λmax also indicated the absence of impurities that could interfere with UV analysis.

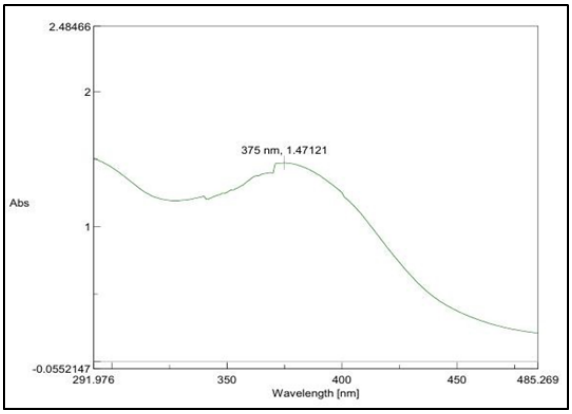

Figure 1: UV spectrum of Lornoxicam in methanol

The solubility profile of Lornoxicam was investigated in different media to assess its dissolution characteristics. The drug showed maximum solubility in methanol (4125 µg/mL), whereas its solubility in aqueous media, including distilled water, acidic buffer (pH 1.2), and phosphate buffers (pH 6.8 and 7.4), was considerably lower. The lowest solubility was observed in distilled water (122 µg/mL), while a slight increase in solubility was noted under neutral and slightly alkaline conditions. These findings confirm that Lornoxicam is a Biopharmaceutical Classification System (BCS) Class II drug, characterized by low aqueous solubility and high permeability. Since poor solubility is the major limiting factor for oral absorption, formulation approaches such as nanoparticle-based drug delivery are expected to improve dissolution behavior and enhance bioavailability.

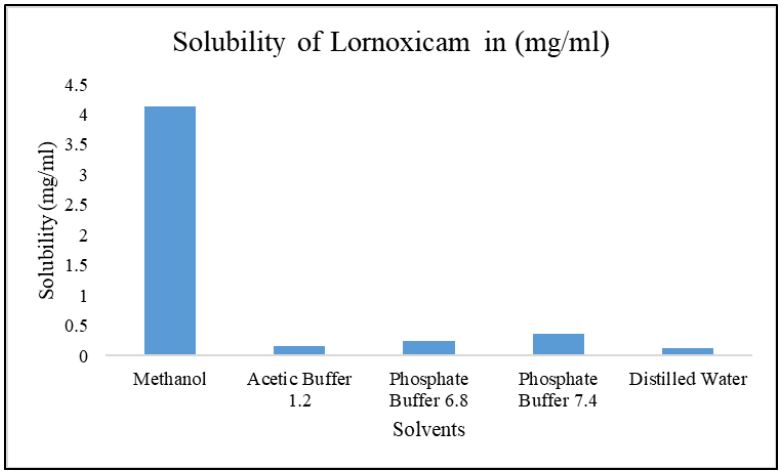

Figure 2: Solubility of drug in mg/ml

Calibration curves of Lornoxicam were prepared in methanol, distilled water, phosphate buffer (pH 6.8 and 7.4), and acidic buffer (pH 1.2) over the concentration range of 10–60 µg/mL. The absorbance increased proportionally with increasing drug concentration in all media, demonstrating good linearity within the selected concentration range. The low standard deviation values obtained for replicate measurements indicated excellent precision and reproducibility of the analytical method. Therefore, the developed UV spectrophotometric method was considered suitable for quantitative estimation of Lornoxicam during formulation and evaluation studies.

Fourier Transform Infrared (FTIR) spectroscopy was performed to confirm the structural integrity of Lornoxicam. The characteristic absorption peaks corresponding to O–H stretching, C=N stretching, aromatic C=C stretching, C–N stretching, C–O stretching, C–Cl stretching, and aromatic C–H bending were observed within their respective reported ranges. The presence of all

characteristic functional groups without any significant shift confirmed the chemical identity and purity of the drug. These results indicated that the drug retained its molecular structure and was suitable for further compatibility and formulation studies.

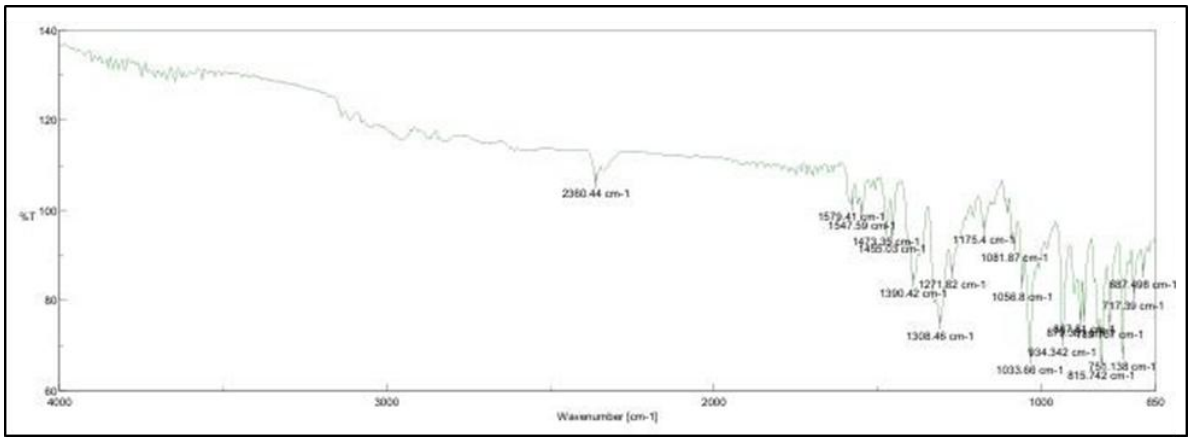

Figure 3: FTIR spectrum of Lornoxicam

The crystalline nature of Lornoxicam was further confirmed by X-ray diffraction (XRD) analysis. The diffraction pattern exhibited several sharp and intense peaks, particularly in the 2θ range of 20–30°, indicating a well-defined crystalline lattice structure. The absence of broad peaks suggested negligible amorphous content in the drug sample. Although crystalline drugs generally exhibit lower aqueous solubility than amorphous forms, maintaining the crystalline nature of Lornoxicam before formulation is advantageous for ensuring its stability. The reduced crystallinity expected after nanoparticle formulation may contribute to improved dissolution and enhanced oral bioavailability.

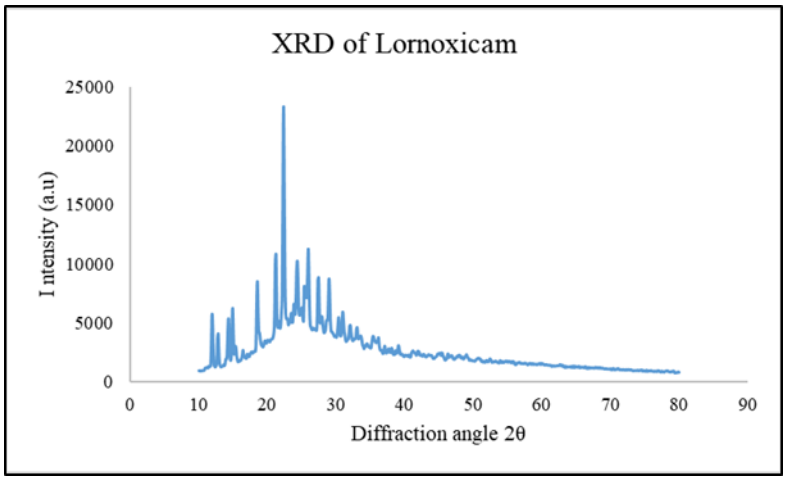

Figure 4: XRD of Lornoxicam

Overall, the preformulation studies established the identity, purity, physicochemical characteristics, and analytical profile of Lornoxicam. The findings confirmed that the drug possesses poor aqueous solubility despite having desirable physicochemical stability, supporting the rationale for developing a nanoparticle-based drug delivery system to improve its dissolution characteristics and therapeutic efficacy.

3.2 Evaluation of Lornoxicam-Loaded Nanoparticles

The prepared Lornoxicam-loaded nanoparticles were evaluated for particle size, polydispersity index (PDI), and zeta potential to assess their physicochemical characteristics and stability. The particle size of all formulations ranged from 124.6 to 207.8 nm**,** indicating successful preparation of nanoparticles within the desired nanoscale range. Among all batches, F10 exhibited the smallest particle size **(**124.6 nm**),** which is expected to enhance drug dissolution and bioavailability.

The PDI values ranged from 0.142 to 0.412, indicating acceptable particle size distribution. The optimized formulation F10 showed the lowest PDI **(**0.142**)**, confirming a narrow and uniform particle size distribution. Zeta potential values ranged from −16.7 to −29.6 mV, suggesting good colloidal stability of the formulations. The highest negative zeta potential was observed for F10 (−29.6 mV), indicating excellent electrostatic stability and reduced particle aggregation.

3.3 Optimization of Nanoparticles

The prepared Lornoxicam-loaded nanoparticles were evaluated for particle size, polydispersity index (PDI), zeta potential, drug content, entrapment efficiency, and percentage yield to identify the optimized formulation.

The particle size of all formulations ranged from **124.6 to 207.8 nm**, indicating successful preparation of nanoparticles within the desired nanoscale range. The optimized formulation **F10** exhibited the smallest particle size (**124.6 nm**) with the lowest PDI (**0.142**), suggesting a narrow and uniform particle size distribution. Zeta potential values ranged from **−16.7 to −29.6 mV**, indicating good colloidal stability. The highest negative zeta potential was observed for **F10 (−29.6 mV)**, demonstrating excellent electrostatic stability and reduced particle aggregation.

Table 1: Response of Particle size

Source	Sum of Squares	df	Mean Square	F-value	p-value	

Model	6117.09	6	1019.52	5.23	0.0321	significant
A-Lipid conc	1737.55	1	1737.55	8.91	0.0245	
B-Polymer conc	0.9112	1	0.9112	0.0047	0.9477	
C-PVA conc	1295.40	1	1295.40	6.64	0.0419	
AB	25.00	1	25.00	0.1282	0.7326	
AC	49.70	1	49.70	0.2549	0.6317	
BC	3008.52	1	3008.52	15.43	0.0077	
Residual	1170.01	6	195.00			
Cor Total	7287.10	12				

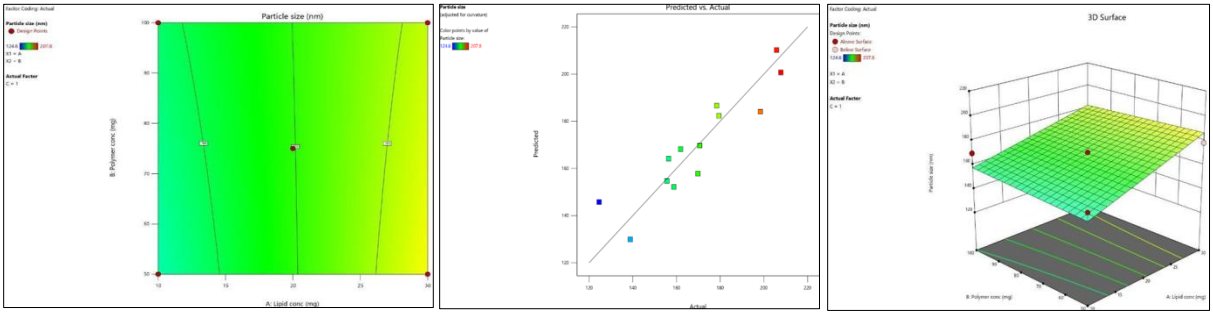

Figure 5: Contour plot for Particle size, Predicted vs actual plot for Particle size, 3D Surface plot for Particle size

Table 2: Response 2 Zeta potential

Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**	
Model	165.61	6	27.60	5.09	0.0342	significant
A-Lipid conc	0.7200	1	0.7200	0.1327	0.7282	
B-Polymer conc	0.0312	1	0.0312	0.0058	0.9420	
C-PVA conc	7.80	1	7.80	1.44	0.2758	
AB	86.49	1	86.49	15.94	0.0072	
AC	70.56	1	70.56	13.00	0.0113	
BC	0.0025	1	0.0025	0.0005	0.9836	
Residual	32.56	6	5.43			
Cor Total	198.17	12				

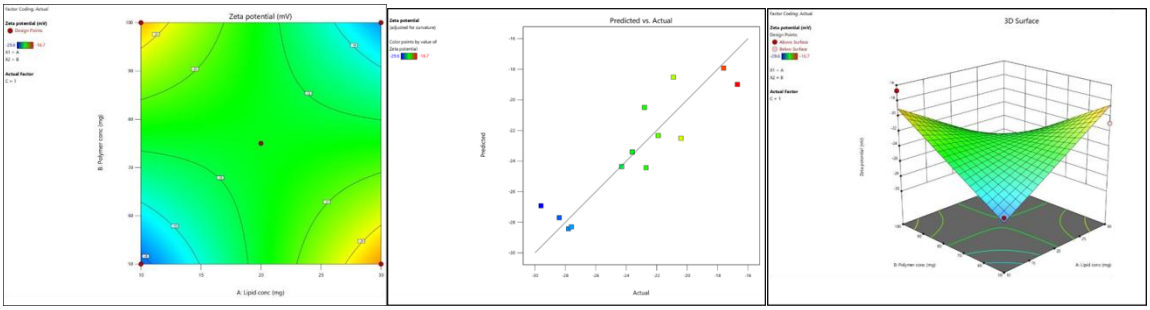

Figure 6: Contour plot for zeta potential, Predicted vs actual plot for zeta potential, 3D surface plot for zeta potential

Statistical optimization using the **Box–Behnken Design (2FI model)** showed that the developed model for particle size was significant (**p = 0.0321**). Lipid concentration (A), PVA concentration (C), and the interaction between polymer and PVA concentration (BC) significantly influenced particle size. The contour plots and 3D response surface plots demonstrated the combined effects of formulation variables on particle size, while the predicted versus actual plot confirmed good agreement between experimental and predicted values.

Drug content analysis showed efficient incorporation of Lornoxicam in all formulations, ranging from **82.26% to 94.26%**. Formulation **F10** exhibited the highest drug content (**94.26%**), indicating superior drug loading capacity. ANOVA results revealed that the developed model was statistically significant (**p = 0.0293**), with the interaction between lipid concentration and PVA concentration (AC) having a significant effect on drug content. The predicted and experimental values showed close agreement, confirming the reliability of the optimization model.

Table 3: Drug content of F1-F13

Formulation code	Drug content (%)
F1	88.22±0.002
F2	87.45±0.001
F3	82.26±0.001
F4	85.26±0.003
F5	83.42±0.002
F6	85.74±0.002
F7	90.86±0.003
F8	88.51±0.001
F9	89.63±0.003
F10	94.26±0.003

F11	86.74±0.004
F12	92.85±0.001
F13	87.74±0.002

The entrapment efficiency of the nanoparticles ranged from **75.64% to 86.23%**, indicating effective encapsulation of Lornoxicam within the polymeric matrix. Among all formulations, **F10** showed the highest entrapment efficiency (**86.23%**), whereas F6 exhibited the lowest value (**75.64%**). The high entrapment efficiency observed in F10 may be attributed to the optimized ratio of lipid, polymer, and stabilizer, which enhanced drug retention during nanoparticle formation.

Response 4: Drug content

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	120.16	6	20.03	5.44	0.0293	significant
A-Lipid conc	0.1891	1	0.1891	0.0513	0.8283	
B-Polymer conc	0.8256	1	0.8256	0.2241	0.6527	
C-PVA conc	17.40	1	17.40	4.72	0.0727	
AB	0.3481	1	0.3481	0.0945	0.7689	
AC	95.94	1	95.94	26.04	0.0022	
BC	5.45	1	5.45	1.48	0.2695	
Residual	22.10	6	3.68			
Cor Total	142.27	12				

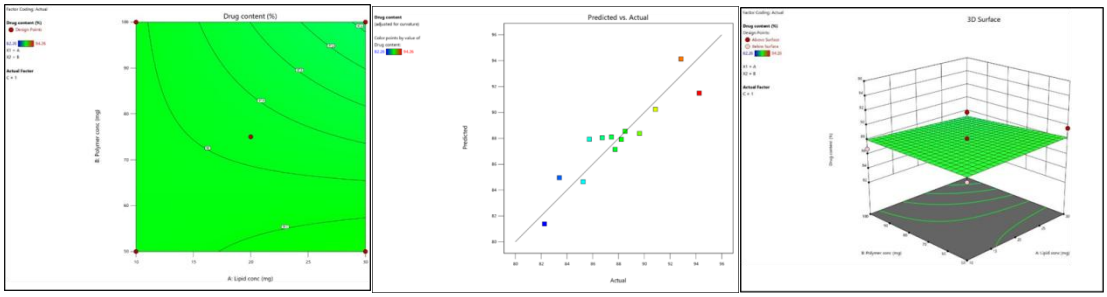

Figure 7: Contour plot for drug content, Predicted vs actual plot for drug content & 3D surface plot for drug content

The percentage yield of the prepared nanoparticles varied between **89.32% and 95.85%**, reflecting good process efficiency and reproducibility. Formulation **F10** exhibited the highest percentage yield (**95.85%**), indicating minimal material loss during preparation. The consistently

high yields obtained for most formulations confirmed the suitability of the nanoprecipitation method for producing Lornoxicam-loaded nanoparticles.

3.4 In Vitro Drug Release and Release Kinetics

The in vitro drug release study was performed to evaluate the release behavior of Lornoxicam from the prepared nanoparticle formulations. All formulations exhibited a sustained drug release pattern over a period of **300 minutes**, with cumulative drug release ranging from **83.10% to 94.88%**. Among all formulations, **F10** showed the highest cumulative drug release (**94.88%**), followed by F6 (93.11%) and F3/F7 (91.99%), indicating efficient drug diffusion from the nanoparticle matrix. The sustained release profile observed in the optimized formulation is expected to improve therapeutic efficacy by maintaining drug levels for a prolonged period while minimizing frequent dosing.

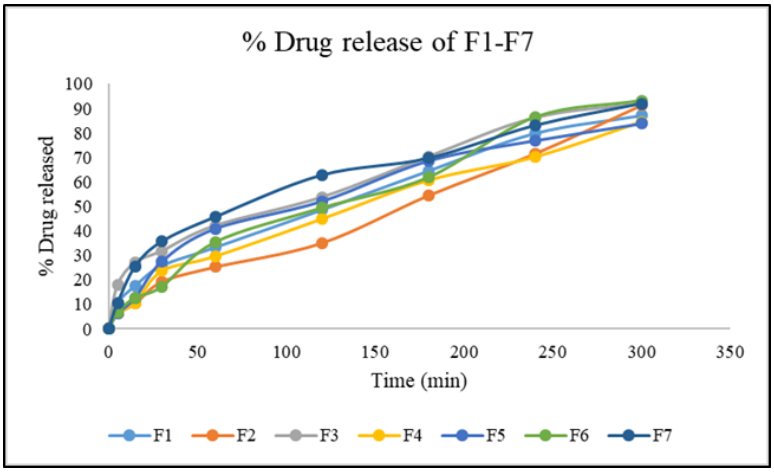

Figure 8: In vitro drug release of F1-F7

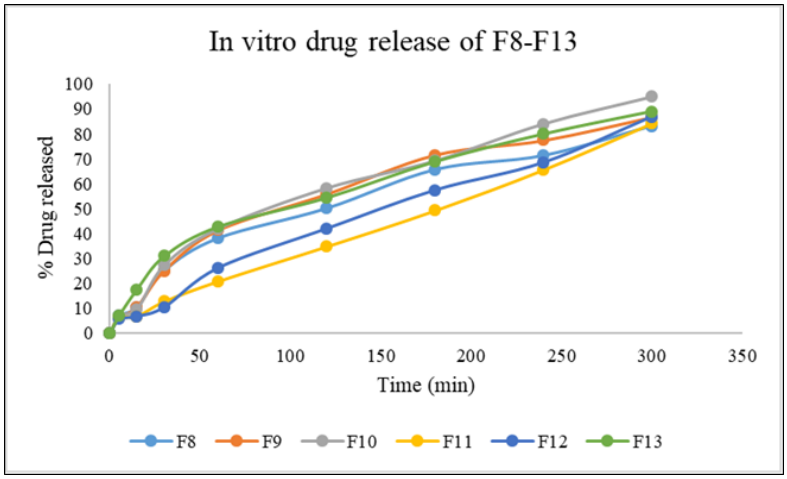

Figure 9: In vitro drug release of F8-F13

To understand the drug release mechanism, the release data of the optimized formulation (F10) were fitted to different kinetic models, including **Zero-order, First-order, and Higuchi models**. The regression coefficient (**R^2**) values obtained were **0.9406** for Zero-order, **0.5944** for First-order, and **0.9902** for the Higuchi model. The highest R^2 value obtained with the Higuchi model indicated that the drug release followed a **diffusion-controlled mechanism**, where the drug diffused gradually through the polymeric matrix. The lower R^2 value of the First-order model suggested that the release was not concentration-dependent.

3.5 FTIR, XRD and Stability Studies

FTIR Analysis:

The FTIR spectrum of the optimized formulation (F10) exhibited all the characteristic peaks of Lornoxicam, including O–H, C–H, C=C/C=N, and C–O/C–Cl functional groups. No significant shift or disappearance of these peaks was observed, indicating the absence of any chemical interaction between the drug and excipients. These findings confirm the compatibility of Lornoxicam with the formulation components and demonstrate that the drug retained its chemical integrity after nanoparticle formulation.

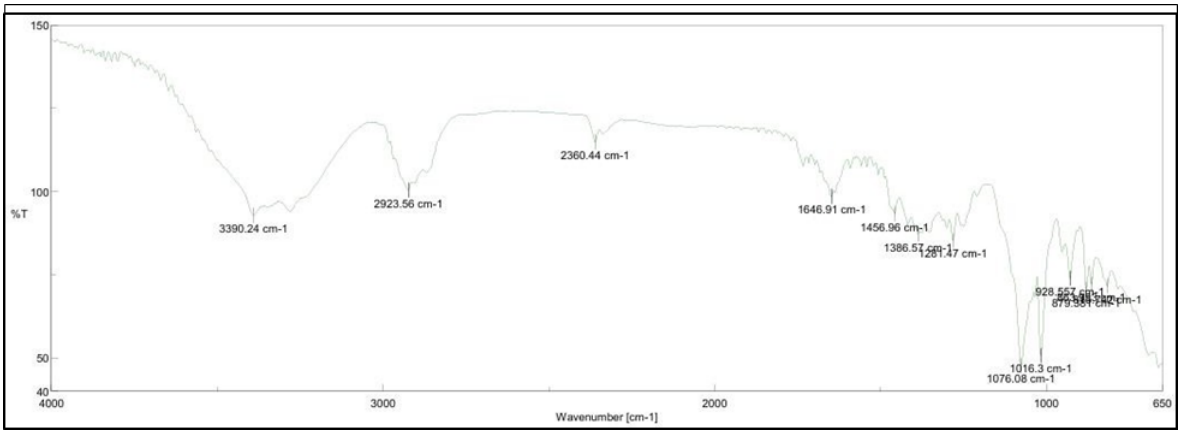

Figure 10: FTIR spectrum of optimized batch F10

XRD Analysis:

The XRD pattern of the optimized formulation (F10) showed broad peaks with reduced intensity, indicating the conversion of the drug from a crystalline to a predominantly amorphous state after encapsulation. The reduction in crystallinity suggests successful incorporation of Lornoxicam

into the nanoparticle matrix, which is expected to improve its solubility, dissolution rate, and overall bioavailability.

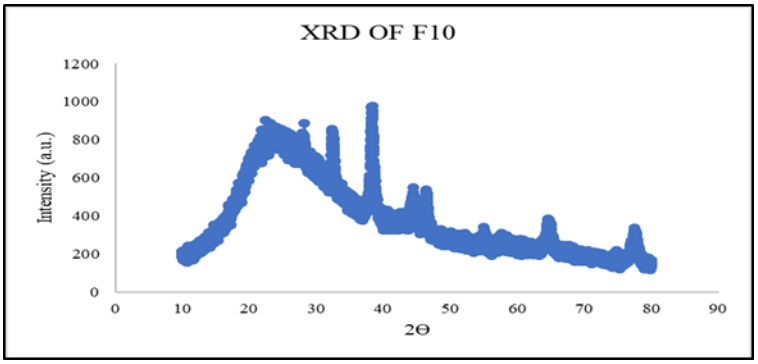

Figure 11: XRD of optimized batch F10

Stability Study:

The optimized formulation (F10) was evaluated for stability over 3 months by monitoring particle size, zeta potential, and drug content. Only slight changes were observed, with particle size increasing from 124.6 to 126.7 nm, zeta potential remaining highly negative (−29.6 to −28.7 mV), and drug content decreasing marginally from 94.26% to 91.85%. These results indicate that the formulation maintained its physicochemical properties throughout the study period. Overall, F10 demonstrated excellent physical and chemical stability, confirming its suitability for long-term storage and further pharmaceutical applications.

4. CONCLUSION

Lornoxicam-loaded polymer–lipid hybrid nanoparticles were successfully formulated using nanoprecipitation, combining Eudragit RL100, Compritol ATO 888, and PVA. The QbD approach and Box–Behnken design allowed systematic optimization of critical formulation parameters, leading to nanoparticles with desirable size, uniformity, surface charge, and drug loading. Batch F10, with small particle size (124.6 nm), low PDI (0.142), and high zeta potential (-29.6 mV), was identified as the optimized formulation suitable for enhancing bioavailability. FTIR and XRD studies confirmed the compatibility of drug and excipients, and the crystalline nature of the drug was preserved. In vitro drug release studies demonstrated sustained release, indicating the potential of the nanoparticles to maintain therapeutic levels and reduce dosing frequency. Stability studies confirmed the robustness of the optimized formulation under accelerated and long-term storage

conditions. Overall, the study demonstrates that polymer–lipid hybrid nanoparticles are a promising strategy to enhance solubility, stability, and bioavailability of Lornoxicam, offering a potential improvement over conventional dosage forms.

5. ACKNOWLEDGEMENTS

The authors express their sincere gratitude to the management and faculty of Dnyan, Kala, Krida, & Krishi Pratishthan's Late Laxmibai Phadtare College Of Pharmacy for providing the necessary facilities and continuous support to carry out this research work. The authors are also thankful to Sai Pharma Research Laboratory Pvt. Ltd., Pune, for providing laboratory facilities and technical assistance during the study. Special thanks are extended to all faculty members, laboratory staff, and colleagues for their valuable guidance, encouragement, and cooperation throughout the research. The authors also acknowledge the support received from family and friends for their constant motivation and encouragement during the completion of this work.

6. CONFLICT OF INTEREST

The authors declare no conflict of interest.

7. REFERENCES

a. Sinko PJ. Martin's Physical Pharmacy and Pharmaceutical Sciences. 7th ed. Philadelphia: Wolters Kluwer Health; 2017.

b. Aulton ME, Taylor KMG. Aulton's Pharmaceutics: The Design and Manufacture of Medicines. 6th ed. London: Elsevier; 2022.

c. Allen LV, Popovich NG, Ansel HC. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. 11th ed. Philadelphia: Lippincott Williams & Wilkins; 2020.

d. Indian Pharmacopoeia Commission. Indian Pharmacopoeia. Vol. I. Ghaziabad: IPC; 2022.

e. ICH Harmonised Guideline. Q1A(R2): Stability Testing of New Drug Substances and Products. Geneva: International Council for Harmonisation; 2003.

f. Higuchi T. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963;52(12):1145–9.

g. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm. 1983;15(1):25–35.

h. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. Pharm Acta Helv. 1985;60(4):110–1.

i. Danaei M, Dehghankhold M, Ataei S, Hasanzadeh Davarani F, Javanmard R, Dokhani A, et al. Impact of particle size and polydispersity index on the clinical applications of lipidic nanocarrier systems. Pharmaceutics. 2018;10(2):57.

j. Bhattacharjee S. DLS and zeta potential—What they are and what they are not? J Control Release. 2016;235:337–51.

k. Müller RH, Mäder K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery—A review of the state of the art. Eur J Pharm Biopharm. 2000;50(1):161–77.

l. Mohanraj VJ, Chen Y. Nanoparticles—A review. Trop J Pharm Res. 2006;5(1):561–73.

m. Parhi R. Drug–excipient compatibility studies by FTIR spectroscopy. J Adv Pharm Educ Res. 2011;1(4):183–90.

n. Shah VP, Tsong Y, Sathe P, Liu JP. In vitro dissolution profile comparison—Statistics and analysis of the similarity factor, f2. Pharm Res. 1998;15(6):889–96.

o. Kesisoglou F, Panmai S, Wu Y. Nanosizing—Oral formulation development and biopharmaceutical evaluation. Adv Drug Deliv Rev. 2007;59(7):631–44.

p. Patravale VB, Date AA, Kulkarni RM. Nanosuspensions: A promising drug delivery strategy. J Pharm Pharmacol. 2004;56(7):827–40.

q. Charman WN, Charman SA. Oral modified-release delivery systems. In: Florence AT, Siepmann J, editors. Modern Pharmaceutics. 5th ed. New York: CRC Press; 2009. p. 273–310.

r. Jain NK. Advances in Controlled and Novel Drug Delivery. 2nd ed. New Delhi: CBS Publishers & Distributors; 2017.