Design and Characterization of Nanostructured Lipid Carrier of Poorly Water Soluble Drug for Improvement of Bioavailability

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Abstract:
Oxaprozin is a nonsteroidal anti-inflammatory drug (NSAID) belonging to the Biopharmaceutics Classification System (BCS) Class II, characterized by poor aqueous solubility despite high permeability. Its limited water solubility results in a slow dissolution rate, delayed onset of action, and reduced oral bioavailability, which can compromise its therapeutic efficacy. Therefore, developing an effective drug delivery system to enhance the solubility and bioavailability of oxaprozin remains an important pharmaceutical challenge. The present study aimed to design and characterize a nanostructured lipid carrier (NLC) formulation of oxaprozin to improve its solubility, dissolution behavior, and oral bioavailability. Nanostructured lipid carriers were developed using a blend of solid and liquid lipids stabilized with suitable surfactants through high-shear homogenization followed by ultrasonication. The formulation variables were optimized to obtain nanoparticles with desirable physicochemical properties and high drug encapsulation. The prepared NLCs were comprehensively characterized for particle size, polydispersity index (PDI), zeta potential, drug loading, entrapment efficiency, morphology, thermal behavior, crystallinity, and in vitro drug release. The optimized formulation exhibited nanosized particles with a narrow size distribution, high encapsulation efficiency, and acceptable zeta potential, indicating good physical stability. Differential scanning calorimetry (DSC) and X-ray diffraction (XRD) analyses confirmed the successful incorporation of oxaprozin into the lipid matrix with a reduction in its crystalline nature, contributing to improved drug solubility. In vitro dissolution studies demonstrated a significantly enhanced drug release profile from the optimized NLC formulation compared with pure oxaprozin, owing to the increased surface area and partial amorphization of the drug within the lipid matrix. The sustained release characteristics of the NLCs further suggested their potential to maintain therapeutic drug concentrations over an extended period. Pharmacokinetic evaluation indicated that the optimized NLC formulation improved the oral bioavailability of oxaprozin by enhancing its dissolution rate and intestinal absorption. The lipid-based nanocarrier system also has the potential to facilitate lymphatic transport and reduce first-pass metabolism, thereby improving systemic drug exposure. Overall, the findings of this study demonstrate that nanostructured lipid carriers are a promising and effective approach for enhancing the solubility, dissolution, and oral bioavailability of poorly water-soluble oxaprozin. The developed formulation may improve therapeutic efficacy while reducing dose-related variability, making NLCs a suitable delivery platform for oxaprozin and other poorly water-soluble drugs.

Keywords: Oxaprozin, Nanostructured Lipid Carrier (NLC), Poorly Water-Soluble Drug, Solubility Enhancement, Oral Bioavailability, Lipid Nanoparticles.

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Introduction

Oral drug delivery remains the most preferred route of drug administration because of its convenience, patient compliance, cost-effectiveness, and ease of manufacturing. However, the therapeutic effectiveness of orally administered drugs is often limited by poor aqueous solubility, which adversely affects drug dissolution and absorption in the gastrointestinal tract. According to the Biopharmaceutics Classification System (BCS), approximately 40–70% of newly developed drug molecules belong to BCS Class II or Class IV and exhibit poor water solubility. Among these, BCS Class II drugs possess high membrane permeability but low aqueous solubility, making dissolution the rate-limiting step in their absorption. Consequently, improving the solubility and dissolution rate of poorly water-soluble drugs has become a major focus in pharmaceutical formulation research.[1,2]

Oxaprozin is a propionic acid derivative belonging to the nonsteroidal anti-inflammatory drug (NSAID) class. It is widely prescribed for the treatment of rheumatoid arthritis, osteoarthritis, musculoskeletal

disorders, and other inflammatory conditions due to its potent analgesic, anti-inflammatory, and antipyretic activities. Oxaprozin exhibits a relatively long elimination half-life, allowing once-daily administration and improved patient compliance. Despite these therapeutic advantages, oxaprozin is classified as a poorly water-soluble drug (BCS Class II), exhibiting limited aqueous solubility but high intestinal permeability. Its poor solubility results in slow dissolution, delayed onset of action, variable gastrointestinal absorption, and reduced oral bioavailability, thereby limiting its therapeutic potential.[3,4]

Several formulation approaches have been investigated to overcome the solubility limitations of poorly water-soluble drugs, including particle size reduction, micronization, nanosuspensions, solid dispersions, cyclodextrin complexation, co-crystals, self-emulsifying drug delivery systems (SEDDS), liposomes, polymeric nanoparticles, and lipid-based nanocarriers. Among these techniques, lipid-based nanocarriers have gained considerable attention because of their ability to improve drug solubilization, protect the encapsulated drug from degradation, enhance intestinal absorption, and potentially facilitate lymphatic transport, thereby reducing hepatic first-pass metabolism.[5,6]

Nanostructured lipid carriers (NLCs) represent the second generation of lipid nanoparticles developed to overcome the limitations associated with solid lipid nanoparticles (SLNs). NLCs consist of a mixture of solid and liquid lipids stabilized by suitable surfactants, resulting in a less ordered lipid matrix with numerous imperfections. This imperfect crystalline structure provides greater space for drug incorporation, leading to higher drug loading, improved entrapment efficiency, reduced drug expulsion during storage, and enhanced formulation stability. Furthermore, the nanoscale particle size increases the surface area available for dissolution, promoting rapid drug release and improved absorption across the gastrointestinal membrane.

The unique properties of nanostructured lipid carriers make them highly suitable for delivering poorly water-soluble drugs such as oxaprozin. The lipid matrix enhances drug solubilization while maintaining the drug in a molecularly dispersed or partially amorphous state, thereby significantly increasing its apparent solubility and dissolution rate. In addition, the presence of physiological lipids improves biocompatibility and minimizes toxicity compared with many synthetic polymer-based delivery systems. The small particle size also promotes close interaction with the intestinal epithelium, which may enhance drug permeation and oral bioavailability.[7]

The physicochemical characteristics of NLCs greatly influence their performance and therapeutic efficacy. Therefore, comprehensive characterization of the developed formulation is essential to ensure its quality and stability. Important characterization parameters include particle size, polydispersity index (PDI), zeta potential, drug loading, entrapment efficiency, surface morphology, thermal behavior, crystallinity, in vitro drug release, and stability studies. Analytical techniques such as dynamic light scattering (DLS), transmission electron microscopy (TEM) or scanning electron microscopy (SEM), differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), and dissolution studies provide valuable information regarding the structural and functional properties of the developed nanocarrier system.

Enhancing the oral bioavailability of oxaprozin through nanostructured lipid carrier technology has the potential to improve therapeutic outcomes by increasing drug solubility, accelerating dissolution, improving gastrointestinal absorption, and maintaining sustained drug release. Such improvements may reduce dose variability, minimize gastrointestinal adverse effects associated with higher doses, and enhance patient compliance. Moreover, NLCs offer advantages such as ease of large-scale production, excellent physical stability, biodegradability, and compatibility with industrial manufacturing processes, making them attractive candidates for commercial pharmaceutical development.[8]

In view of these considerations, the present study aims to design, formulate, and characterize nanostructured lipid carriers of oxaprozin to improve its aqueous solubility and oral bioavailability. The prepared formulations will be optimized and evaluated for their physicochemical properties, drug encapsulation efficiency, particle size distribution, surface charge, morphology, thermal behavior, crystallinity, in vitro drug release, and stability. The study is expected to demonstrate the potential of nanostructured lipid carriers as an effective delivery system for improving the therapeutic performance of poorly water-soluble oxaprozin and may provide a promising platform for the oral delivery of other poorly soluble drugs.[9,10]

Methodology

Formulation characterization and optimization of nanostructured lipid carriers

Screening of excipients

i) Selection of solid lipids

The solid lipid having higher solubility of oxaprozin was chosen for the formulation of nanostructured lipid carriers (NLC). Drug solubility was studied in solid lipids such as glycerol mono stearate and hydrogenated vegetable oil. For saturation solubility study, 1 gm of each solid lipid was transferred into a glass vial immersed in the water bath (5°C greater than melting point of solid lipids) Subsequently, the vials containing melted lipid were flooded with excess drug up to build a saturation concentration. A saturated solid lipid and drug mixture was then added to the vial containing 5 ml of methanol (methanol is used as solvent as oxaprozin completely soluble in methanol). The mixture was stirred for 24 hrs using mechanical

stirring at 100 rpm. The supernatant was filtered through 0.45 µ filter paper. Screens by UV spectrophotometer for diluents.[11,12]

ii) Selection of liquid lipids

In the current study, miglyol 812 was chosen as liquid lipid for developing oxaprozin nanostructeured lipid carriers. Then the oxaprozin was dissolved in miglyol 812 and stirred for 30 min at room temperature using magnetic stirrer. Visual evaluation of drug solubility in miglyol 812. It dissolved everything, leading to clear solution.[13,14]

Optimization of nanostructured lipid carriers Box behnken design of experiment

Statistical design of experiment is based on Box behenken method of optimization was used in present study. In this experiment, a total of 17 runs were performed with three factors and four levels. Design of experiment Design-Expert software was utilized for the purpose. In this study, this software was used to optimize the raw materials and mixture composition (Design-Expert 12.0, State-Ease Inc., Minneapolis, USA)

Batches of thermoresponsive oxaprozin loaded nanostructured lipid carriers were formulated by using response surface methodology (RSM) designs to optimize the influence of independent variables upon NLC properties. Independent variables include total lipid concentration (X 1), liquid lipid-to-solid lipid ratio (X 2) and surfactant concentration (X 3).

The independent variables included in this study: Physico–chemical characteristics of the formulated NLC, i.e., mean particle size (Y1), zeta potential (Y2) and entrapment efficiency % (Y3) & drug loading (Y4). A (-1) sign and (+1) sign were used to designate lower and upper values for the various factors. The optimization model has used the directed response surface methodology in order to minimize the utilization of experiments to optimized drug loaded NLC.

Variables in Box–Behenken Response Surface Method) design for formulation of oxaprozin NLC using design expert 12.0.9.0. The optimization process was performed using systematic formulation steps to minimize trials and analyze response surfaces to influence the fundamental effects of factors in order to obtain suitable formulations with desired goals efficiently.

Thus, to achieve the best formulations efficiently in desired parameters (EE, DL, zeta potential and particle size) of oxaprozin nanostructured lipid carrier, response surface methodology was applied.[15,16]

Table 1: Factors and responses used in Box–Behnken design

Factor	**Level Used**
Independent variable (For ND1- ND17)	
X1- Total	
	1%
	1.5%
	2%
lipid concentration	
X2- liquid lipid to	
	15%
	30%
	45% solid lipid ratio
X3- Surfactant	
	1%
	1.5%
	2%
Concentration	

Dependent variable for all batches	
Y1- Mean particle size	
Minimize	
Y2- Zeta Potential	
Maximise	
Y3- Entrapment Efficiency %	
Maximize	
Y4- Drug Loading %	
Maximize	

Formulation of Oxaprozin-loaded nanostructured lipid carriers (ND1 to ND17)

With some modifications high pressure method was used to fabricate 17 different homogenization Oxaprozin-loaded nanostructured lipid carriers, ND1 to ND17. Nanostructured lipid carriers ND1 to ND17 were formulated with 0.05 % drug loading; ie.50 mg oxaprozin per100 mlof these formulations . Glyceryl mono stearate (GMS), miglyol 812, acrysol El 135 was used as solid lipid, liquid lipid and surfactant respectively. They have been mixed with liquid readily fluid and solid readily fluid in different proportions.[17,18]

Methodology

Design of experiments for NLC using Box Behenken model Modified high pressure homogenization method used to formulate oxaprozin nanostructured lipid carrier. First solid lipid GMS was melt at approximately 60° – 62°C and Miglyol 812 was added, that mixed even. Oxaprozin is heat sensitive drug. The temperature of the lipid mixture was decreased by cooling at room temperature. A weighed amount of drug (50 mg) was added to this lipid mixture and mixed so as to form a lipid phase. A separate aqueous phase was created by dissolving Acrysol EL 135 in distilled water. A mechanical stirrer was used to transfer the lipid phase into aqueous surfactant at 1500 rpm with constant stirring for 30 min. This led to the formation of a pre-emulsion. High pressure homogenization (5–7 cycles, 600 to 800 bars) was applied to the formed pre-emulsion allowing the formation of nanostructured lipid carriers. Lastly, the dried (solid NLC) was obtained from resultant nanostructured lipid carrier suspension by freeze drying. The % drug loading and % entrapment efficiency of freeze dried NLC were determined. [19]

Determination of Entrapment efficiency

Entrapment efficiency of oxaprozin in NLCs For entrapment efficiency determination, 2 ml of drug loaded NLC dispersion (ND1 to ND17) were centrifuged at 10,000 RPM for 45 minute to separate lipid phase and aqueous phase. For free drug in the aqueous phase, supernatant (1 ml) was diluted with a methanol and after passing through 0.45 micron filter paper, concentration of drug was measured by UV spectrophotometer. Free drug concentration in aqueous phase was calculated. The concentration of total drug oxaprozin in NLC dispersion (1ml) were lyophilised with help of freeze dryer. The solid NLC was re-suspended in methanol and then the concentration of drug was determined in diluted NLC using UV spectrophotometer.[20,21]

ii) Determination of drug loading

To perform the determination of drug loading 1 ml of each drug loaded nanostructured lipid carrier were taken and freeze dried for 12 hrs, weight of lyophilized NLC formulation was measured. Resuspended in methanol Further, solid NLC were filtered using 0.45 micron filter paper and the drug concentration was measured by UV spectrophotometer. The amount of drug entrapped in NLC was estimated and the percentage Drug loading (%) was calculated.[22]

iii) Particle size analysis and Zeta potential

Dynamic light scattering technique, Zetasizer Nano Plus (Malvern Instruments, Malvern, Worcestershire UK) was used to measure the particle size and zeta potential. The NLC dispersion was diluted ten times before measurement of sizes and zeta potentials by using distilled water at 25°C. Standard laser 4 mW He–Ne, 633 nm was used at fixed angle of measurement (90°).[23]

iv) Polydispersibility index (PDI)

Dispersibility of the developed formulations: Polydispersity index The polydispersity index was performed on all NLC formulations to give a clearer idea about particle size distribution by using a standard polydispersity index formula .[24]

***In vitro* drug release study**

The in vitro release study of drug from plain drug suspension, marketed formulation suspension and optimised NLC were performed using dialysis bag technique. Phosphate buffer pH 7.4 containing 0.8% tween 80 was used for in vitro study as release media. Dialysis bags with MW cut-off 12,000-14,000 (Himedia-Dialysis membrane 135, Mol. To be activated, samples (Molecular weight cut off 12,000–14,000 Da Mumbai, India) were soaked in Phosphate buffer pH 7.4 containing 0.8% tween 80 release medium for 24 hours before study. In vitro release profile of pure drug, marketed formulation

and optimised NLC (equivalent to 5 mg) at a concentration of 0.025 g/ml were filled into separate dialysis bags. The dialysis bags were drown by using 100 ml of release media - phosphate buffer pH 7.4 containing with 0.8% tween 80 in the beaker. The beaker were placed on a magnetic stirrer and stirred at 150 rpm. The temperature was maintained at 37±0.5 °C, and the release media was withdrawn (1 ml) at predetermined intervals of time; that is, 0, 0.5, 1, 2, 4, 6,8,12 and24 h.the same volume was replaced by fresh release media in the beaker continously to avoid changes on sink condition. The studies of release were conducted in triplicate. Release of Free Drug from the Oxaprozin Suspension (0.5 mg/ml) was performed by similar method. The samples were diluted and drug release was analyzed by UV spectrophotometer.[25]

Table2 : Formulation composition of nanostructured lipid carriers (ND1 to ND17)

Form	Total lipid%	Liquid lipid to solid lipid ratio	% of Acrysol
ND1	1.5	15:85	1
ND2	1.5	30:70	1.5
ND3	1.5	15:85	2
ND4	2	30:70	2
ND5	1	30:70	1
ND6	2	15:85	1.5
ND7	1.5	30:70	1.5
ND8	1.5	45:55	1
ND9	1.5	30:70	1.5
ND10	2	45:55	1.5
ND11	1	45:55	1.5
ND12	1	30:70	2
ND13	1.5	45:55	2
ND14	2	30:70	1
ND15	1.5	30:70	1.5
ND16	1.5	15:85	1.5
ND17	1.5	30:70	1.5

***In vivo* pharmacokinetic study for optimised NLC**

As per the protocol, in vivo pharmacokinetic study was performed to investigate bioavailability of oxaprozin after administration of optimized NLC formulation (NLC-D11), marketed suspension and plain oxaprozin suspension. The maximum concentration in plasma (Cmax) and the time required to achieve this concentration (Tmax) of oxaprozin were measured from the oxaprozin plasma drug concentration–time plot. Other parameters such as half life or volume of distribution, etc. were calculated using the software.package.[26]

Result:

i) Solubility of oxaprozin

Table 3 : The solubility of oxaprozin in various surface active agents

Lipid excipients	Solubility (mg/g)
Labrasol	96.999 ± 6.431
Acrysol EL 135/ Cremophor EL	237.78 ± 4.430
Transcutol P	170.03 ± 5. 901

Table 4 : The solubility of oxaprozin in various solid lipids

Solid Lipid excipients	Solubility (mg/g)
Glycerol mono stearate	58.29 ± 2.13
Hydrogenated vegetable oil.	39.03 ± 3.43

Evaluation of Oxaprozin Nanostructured Lipid Carriers (ND1- ND17)

Table 5: Evaluation of Oxaprozin -NLC, ND1-ND17

	Factor			Response			
	X1	X2	X3	Y1	Y 2	Y3	Y4

Run	Total lipid %	liquid lipid to solid lipid	surfactant %	particle size nm	Zeta potential (mV)	drug loading %	EE %
ND1	1.5	15:85	1	238.21 ± 2.34	14.76	3.148	98.56
ND2	1.5	30:70	1.5	202.14 ± 2.46	19.22	2.375	99.60
ND3	1.5	15:85	2	234.42 ± 1.37	17.24	2.187	99.67
ND4	2	30:70	2	187.66 ± 3.14	24.83	1.709	99.80
ND5	1	30:70	1	176.70 ± 2.21	27.45	3.99	97.35
ND6	2	15:85	1.5	240.11 ± 2.11	13.93	3.291	98.84
ND7	1.5	30:70	1.5	196.50 ±1.18	23.75	2.56	98.76
ND8	1.5	45:55	1	186.26 ± 2.46	25.82	2.60	97.23
ND9	1.5	30:70	1.5	198.08 ± 2.26	23.35	2.77	99.56
ND10	2	45:55	1.5	174.12 ± 2.64	27.79	2.32	98.45
ND11	1	45:55	1.5	127.20 ± 2.45	31.45	5.18	99.46
ND12	1	30:70	2	163.18 ± 2.19	26.87	2.54	98.11
ND13	1.5	45:55	2	158.21 ± 1.84	30.43	2.28	98.87
ND14	2	30:70	1	211.10 ± 2.04	19.48	2.32	99.53
ND15	1.5	30:70	1.5	199.31 ±2.17	24.75	2.85	98.50
ND16	1	15:85	1.5	228.19 ± 2.38	16.18	3.121	99.56
ND17	1.5	30:70	1.5	197.70 ± 1.78	26.15	2.48	99.68

Selection of NLC using the Desirability Function

Selection of an optimal NLC – minimum Particle size and maximum DL%, EE%, zeta potential using desirability function The highest desirability values (0.825) were found for NLC, ND-11 formulation.

Percentage drug release through formulation

Table 6 :*In vitro* drug release

Time in min	Percentage drug release through formulation (%)		
	Oxaprozin	**Marketed Product**	**Optimised NLC-ND11**
0	0	0	0
10	0.57± 0.18	8.56 ± 1.02	32.29± 1.23
20	6.9± 1.03	15.45± 1.47	57.57 ± 2.28
30	8.02± 1.06	24.78± 2.74	66.04± 2.36
40	10.69± 1.24	38.45± 2.35	70.34 ± 1.09
50	12.23± 1.21	45.43± 2.46	79.59± 1.84
60	13.58± 1.13	52.47± 2.22	82.39± 2.24
80	15.27± 1.17	59.67± 2.79	93.89± 1.18
100	23.82± 1.08	63.48± 1.22	100.04 ± 2.64

Pharmacokinetic study of nanostructured lipid formulation of oxaprozin

From plasma concentration of the drug versus time profile, Cmax and Tmax was determined directly. Method for calculating the AUC following oral administration of oxaprozin in which trapezoidal area Approximation by linear interpolation was based on an open reference. It belong to BCS class II and has low permeability and poor aqueous solubility, hence novel lipid based nano formulations are needed to develop for this drug .

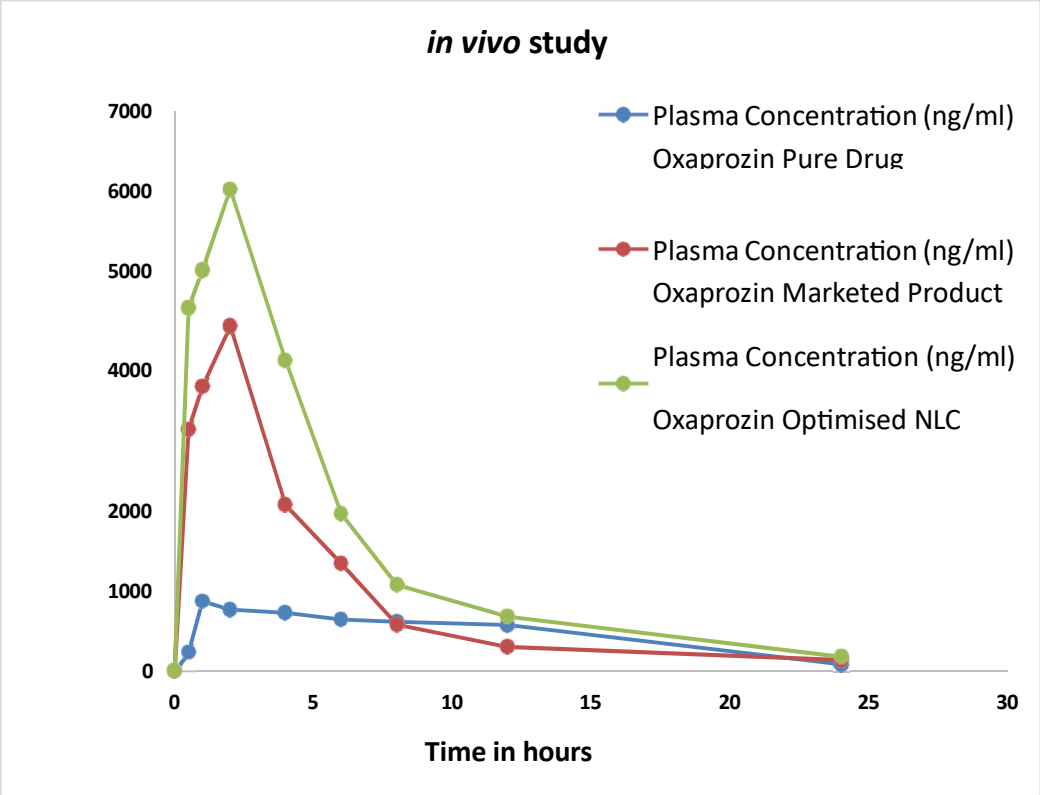

Table 7 : Pharmacokinetic parameters

Parameters	Oxaprozin Pure Drug	Oxaprozin Marketed Product	Oxaprozin optimised NLC
Cmax [ng/ml]	872 ± 21.64	4320 ± 78.36	6030 ± 94.98
Tmax [hrs]	1 ± 0.06	2 ± 0.12	2 ± 0.16
AUC(0-24) [h.ng/ml]	11676.5± 238.12	22521.25 ± 196.18	36560.8 ± 146.23
t 1/2 [hrs]	5.20 ± 0.34	5.55 ± 0.28	6.308 ± 0.26
Vd [L/kg]	2.01594	0.3154	0.1740
Cl [ml/min/kg]	0.4858	0.0346	0.0217
Ke	0.133	0.124	0.109

Table 8 : Relative Bioavailability of NLC-ND11

Relative bioavailability of NLC Vs. marketed tab	**162.33 %**
Relative bioavailability of NLC Vs. pure drug	**313.11 %**
Fold enhancement in bioavailability as compared to pure drug	**3.13 fold enhancement in bioavailability.**
Fold enhancement in bioavailability as compared to marketed tab	**1.62 sfold enhancement in bioavailability.**

Pharmacokinetic parameters (Cmax, Tmax and AUC (0–24) were illustrated with significant differences that promote absorption and drug bioavailability using NLCs. This drug bioavailability was substantially improved in oxaprozin loaded NLCs as demonstrated through pharmacokinetic studies. The relative bioavailability of NLC was found 313.11% as compared to pure drug and also Relative bioavailability of NLC was found 162.33%. Therefore, the bioavailability outcome evaluated by AUC (0-24) demonstrated NLC-ND11 improved bioavailability of 3.13 -fold and 1.62 fold compared with that of drug suspension and market product .

Conclusion:

Nanostructured lipid carriers (NLCs) are advanced lipid-based nanoparticles prepared using a combination of solid and liquid lipids stabilized with surfactants. The imperfect lipid matrix created by mixing different lipids provides greater drug loading capacity and minimizes drug leakage during storage. When oxaprozin is incorporated into NLCs, the nanosized particles increase surface area, improve dissolution, enhance mucoadhesion, and prolong gastrointestinal residence time. NLCs also protect the drug from chemical degradation and provide controlled or sustained drug release, resulting in improved therapeutic efficacy and reduced dosing frequency. Compared with conventional lipid nanoparticles, NLCs offer better physical stability, higher encapsulation efficiency, and greater bioavailability.

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