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"Revolutionizing Bioavailability: Formulation And Assessment Of Nanosuspension For Enhancing The Performance Of PoorlySoluble Drugs"

Pramod Motiram Bhosale[1]*, Dr.Manmeet Singh[2]

1:Ph.D Scholar, Department of Pharmaceutics, SunRise University, Alwar, Rajasthan, India.

2:Ph.D Research Guide & Professor, Department of Pharmaceutics, SunRise University, Alwar, Rajasthan, India.

*Corresponding Author:-Pramod Motiram Bhosale

Ph.D Scholar, Department of Pharmaceutics, SunRise University, Alwar, Rajasthan, India.

Email:- pramodbhosale777@gmail.com

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ABSTRACT:-

Nepafenac, is a potent non-steroidal anti-inflammatory drug (NSAID), was formulated into a nanosuspension using the solvent diffusion method to enhance its ocular drug delivery. Nepafenac was dissolved in ethanol and added drop wise to an aqueous phase containing HPMC E-5 and Poloxamer 407. The mixture was homogenized using a Digital Ultra Turrax homogenizer and then stirred to remove residual solvent. Various formulations (F1 to F9) were prepared with different ratios of stabilizers and surfactants. The nanosuspension was characterized for particle size and Polydispersity Index (PDI) using a Zetasizer. Zeta potential measurements were performed to assess surface charge. The pH of formulations was measured immediately post-preparation. Field Emission Scanning Electron Microscopy (FE-SEM) was used to examine the morphology of the optimized formulation (F7). Viscosity was measured using a Brookfield viscometer. The nanosuspension formulations exhibited particle sizes suitable for intraocular injection, with a narrow size distribution and adequate zeta potential (-11.1 mV) indicating physical stability. The pH of formulations ranged between 6.7 to 7.15. FE-SEM images revealed amorphous particles with spherical morphology. Viscosity ranged from 63 to 94 CPS, increasing with the concentration of stabilizers and surfactants. In vitro drug release profiles showed sustained release over 8 hours, with higher release rates observed at higher drug concentrations. Formulation F7 demonstrated a drug release of 95.15±0.21% at 8 hours. Ex vivo transcorneal permeation studies on goat corneas demonstrated enhanced permeation of Nepafenac from the optimized nanosuspension (91.12±0.71%) compared to a marketed preparation (45.3±0.59%) after 8 hours. Stability of Optimized formulation i.e. F7 was evaluated over 3 months, showing consistent drug release profiles with minimal variation. Initial drug release percentages over 8 hours were maintained after 3 months, indicating stable performance over time. The solvent diffusion method successfully produced Nepafenac Nanosuspension with desirable physicochemical properties and enhanced drug delivery characteristics. Stability studies confirmed sustained drug release profiles, highlighting potential for prolonged therapeutic efficacy in ocular applications.

Keywords: Nanosuspension, Nepafenac, Ocular drug delivery, Drug bioavailability, Formulation optimization, In vitro release, Ex vivo permeation, Drug delivery systems.

INTRODUCTION:-

Ocular drug delivery possess substantial challenges due to anatomical barriers and rapid drug clearance mechanisms, demanding innovative formulations to enhance therapeutic efficacy.[1-2]For ocular issues including inflammation after surgery, the nonsteroidal anti-inflammatory medicine (NSAID) Napafenac is an excellent choice due to its strong anti-inflammatory effects. However, its limited aqueous solubility significantly hinders its bioavailability when administered in conventional eye drops. Nanosuspension, colloidal systems comprising drug nanoparticles, represent a promising strategy to improve drug solubility and bioavailability.[3]Recent advancements in nanotechnology have provided a platform to address the issues associated with poorly soluble drugs like Nepafenac.[4-5]This research aims to develop and characterize Nepafenac loaded nanosuspension to enhance its ocular bioavailability. Despite notable progress in nanosuspension formulations for other drugs, comprehensive investigations specific to Nepafenac nanosuspension for ocular applications are relatively scarce in the current literature.[6]The current literature emphasizes various strategies for ocular drug delivery, including liposomes, nanoparticles, and microemulsions, demonstrating enhanced drug permeation and sustained release profiles. However, despite the therapeutic potential of Nepafenac, studies focusing on its nanosuspension formulations tailored for ocular delivery are limited. Existing research predominantly highlights conventional formulations, failing to address the challenges of poor drug solubility and bioavailability associated with Nepafenac.[7-8]This research intends to bridge this gap by systematically preparing, characterizing, and evaluating Nepafenac loaded nanosuspension. Important features of these nanosystems, including their shape, zeta potential, particle size, and in vitro/in vivo performance, are the focus of the inquiry. Understanding these parameters can elucidate the potential of nanosuspension in enhancing Nepafenac's ocular bioavailability, which remains a critical unexplored area in current ocular drug delivery research.[9-10]Overall, this study seeks to contribute significantly to the development of innovative ocular drug delivery systems by addressing the research gap concerning Nepafenac loaded nanosuspension, potentially paving the way for improved therapeutic outcomes in ocular diseases.

MATERIALS AND METHODS:-

Materials:

The materials used in formulating a Nepafenac nanosuspension via the solvent diffusion method include Nepafenac as the active pharmaceutical ingredient, 5 ml of ethanol as the organic solvent, HPMC E-5 as a stabilizer, Poloxamer 407 as a surfactant.

Preparation of Nanosuspension:

To prepare a Nepafenac nanosuspension using the solvent diffusion approach, dilute a precise quantity of Nepafenac in 5ml of ethanol. Gradually administer this solution into a 25ml aqueous phase containing HPMC E-5 and Poloxamer 407 using a syringe equipped with a 24-gauge needle. Use a Digital Ultra Turrax homogenizer to blend the mixture at a speed of 12,000-18,000 rpm for duration of 10-20 minutes. Next agitate the mixture using a magnetic stirrer for duration of 2 to 3 hours in order to remove any leftover solvent by evaporation. This procedure guarantees the even dispersion of Nepafenac and the elimination of the solvent, hence improving the quality and durability of the end product.[11-12]

Table 1: Composition of Nanosuspension

Batch	Nepafenac	Ethanol	Pluronic	HPMC E-5	Benzalkonium Chloride	Distilled Water
F1	25	7	1.0	0.3	0.01%	q.s
F2	25	7	1.0	0.4	0.01%	q.s
F3	25	7	1.0	0.5	0.01%	q.s
F4	25	7	0.15	0.3	0.01%	q.s
F5	25	7	0.15	0.4	0.01%	q.s
F6	25	7	0.15	0.5	0.01%	q.s
F7	25	7	0.2	0.3	0.01%	q.s
F8	25	7	0.2	0.4	0.01%	q.s
F9	25	7	0.2	0.5	0.01%	q.s

CHARACTERIZATION OF NANOSUSPENSION:-

Coefficient of dispersion and Particle size:

For the purpose of this experiment, we utilizedZetasizer(Version 6.20) in order to determine the size of the Nano particle suspension. The size and Polydispersity Index (PDI) of each batch of Nanosuspension that was created and it was examined under a microscope. A little drop of Nanosuspension solution was placed on a slide at several locations to quantify the size of each batch's. When that was finished, we proceeded to determine the average size of the Nanosuspension as well as its PDI. [13]

Zeta Potential:

For the purpose of determining the charge on both drug free and drug loaded Nanosuspensions, Zetasizer(Version 6.20) was utilised. The Nanosuspension's average zeta potential and charge were calculated after 60 seconds of analysis. This result proves that the produced liposomes have enough charge to contain vesicle aggregation (Nepafenac Nanosuspension) and that anions dominate the surface of the Nanosuspension.[14]

Calculating pH:

Using a calibrated digital pH metre, the pH of each mixture was recorded right after preparation. The formulations pH levels were measured and documented.[15]

Field Emission Scanning Electron Microscopy (FE-SEM):

The morphology and shape of a nanosuspension formulation were examined using FE-SEM(JSM-7610F, Tokyo, Japan, JEOL). To make the samples, enough coarse dust was placed onto glass slides, and then a small drop of the suspension was dropped on top. After that, these slides were attached to an aluminium stub and coated with a 400 A thick coating of fine platinum in an argon atmosphere using a cold sputter coater. Subsequently, 5.0 kV photomicrographs were recorded. [16]

Viscosity:

A nanosuspension formulation's viscosity was measured using a 100 rpm spinder number 61 and a Brookfield viscometer with model number LVPVE. [17]

In Vitro Study:

A Franz diffusion cell was used to investigate the release of nepafenac from a pluronic nanosuspension in a pH 7.4 buffer. The donor and acceptor compartments were separated using a dialysis membrane. Using a magnetic bar for stirring, 5ml of the formulation was moved to the donor compartment, while 21ml of pH 7.4 buffer was introduced to the acceptor compartment. A water bath was used to regulate the temperature of the receptor compartment at 37 ± 0.5°C. At regular intervals, 1ml of the sample was extracted and substituted with an equal amount of new buffer with a pH of 7.4 in order to maintain a stable condition of dilution. The materials underwent spectroscopic analysis at a wavelength of 237.2 nm after being suitably diluted with a buffer solution at pH 7.4.[18]

Ex Vivo Study:

A modified side by side diffusion cell was used to perform ex vivo ocular drug permeation on a goat cornea containing a polymeric Nano solution. After being obtained from the slaughterhouse, the fresh goat eye was preserved in ice cooled PB solution with a pH of 7.4. Within a time frame of 30 minutes after the animal's death, the cornea and a small amount of surrounding scleral tissue measuring 2-4 mm were carefully extracted from the eye using cold saline solution. Once the cornea was wetted and placed with its outer layer towards the donor side, it was inserted between the donor and receptor cells. Upon addition of the polymeric nano suspension to the pH 7.4 buffer, the magnetic stir bars in both the donor and reservoir chambers were adjusted to a constant speed of 250 RPM and stirred continuously. A constant temperature of 34°C was maintained throughout the experiment by use a circulating water bath. The receiver chamber was kept at a steady sink condition for up to 8 hours by repeatedly removing 1ml samples and refilling it with new buffer solution. Analysed samples using a UV spectrophotometer calibrated at a wavelength of 237.2 nm.[19-20]

RESULTS AND DISCUSSION:-

X-Ray diffraction analysis (XRD):

The X-ray diffraction (XRD) analysis of Nepafenac provides critical insights into its crystalline structure. By examining the positions, intensities, and widths of the diffraction peaks, one can identify the specific crystalline phases present in the sample, assess phase purity, and determine the degree of crystallinity. Sharp, well defined peaks indicate high crystallinity, while broader peaks suggest smaller crystallite sizes or internal strain. Comparison with standard reference patterns can confirm the presence of known polymorphic forms of Nepafenac and detect any impurities. These findings are essential for understanding the material's properties and optimizing its pharmaceutical formulation.

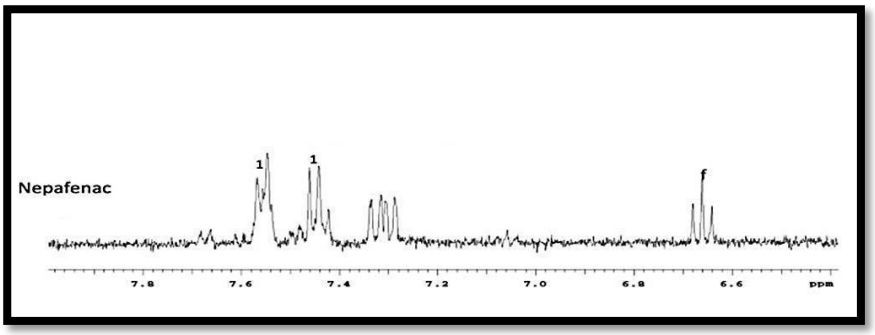

Figure 1: X-ray diffraction (XRD) analysis of Nepafenac

Differential Scanning Calorimetry(DSC):

The DSC thermogram of Nepafenac shows a prominent endothermic peak around 140-150°C, indicating its melting point. This thermal event is critical for assessing the purity and stability of Nepafenac. The initial downward slope near 50-100°C may suggest the loss of water or solvent, while the overall absence of other significant peaks implies no major impurities or phase transitions affecting its thermal behavior. These insights are vital for optimizing Nepafenac's pharmaceutical formulation, ensuring its stability and efficacy.

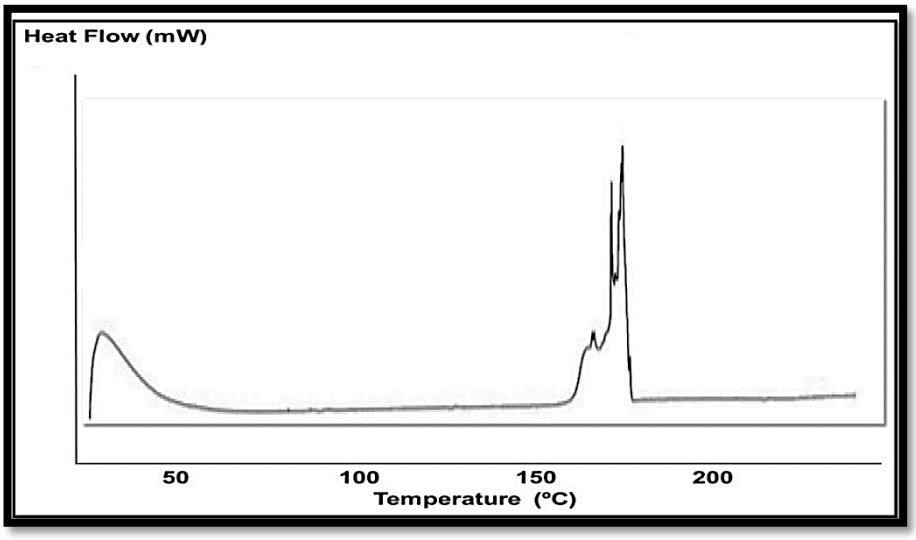

Figure 2: DSC thermogram of Nepafenac

CHARECTERIZATION OF NANOSUSPENSION:-

Coefficient of dispersion and the dimension of particles:

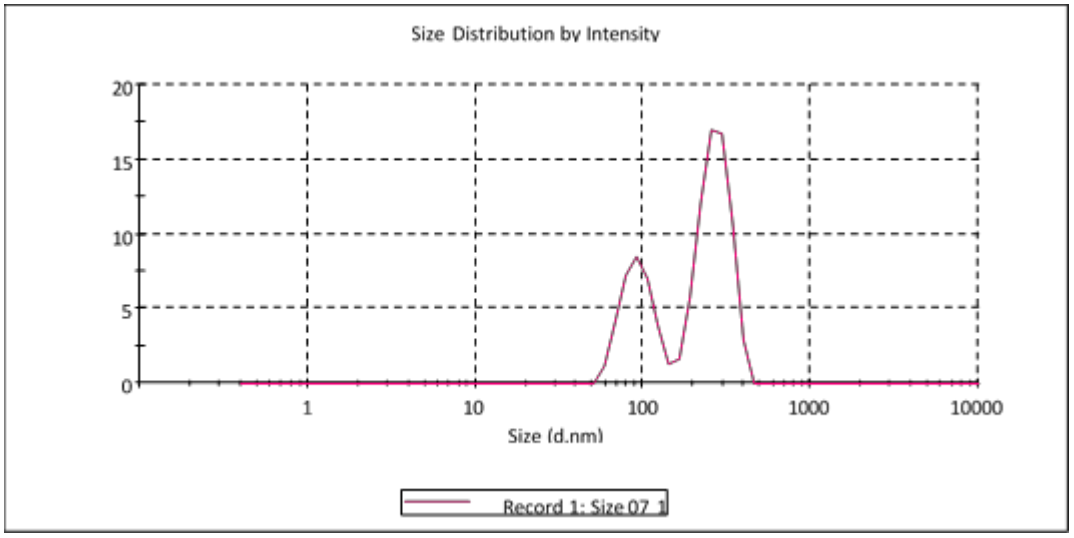

Figure 3: Coefficient of dispersion and the dimension of particles

A motic microscope was used to ascertain the particle size. Under a microscope, we examined the sizes of all the created batches. The above figure shows the results of these pictures, which showed round particles with a very narrow size distribution. The size and appearance of all the particles were just right intraocular for injection.

Zeta Potential:

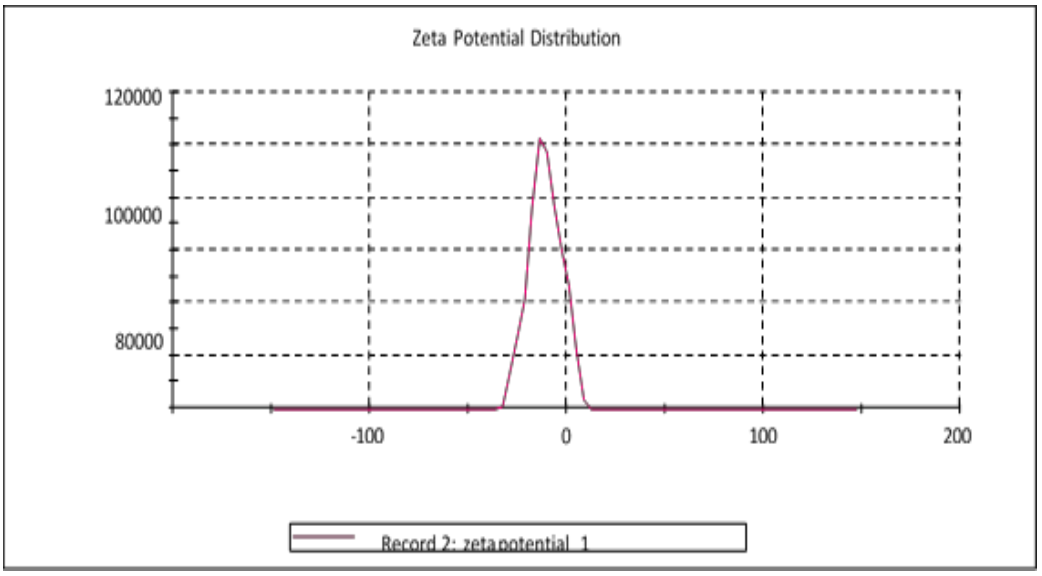

Figure 4: Zeta Potential

An important tool for calculating the surface charges and stability of such particles is the Zeta Potential. The nanosuspension is in its most physically stable condition, as shown by the zeta potential measurement of -11.1.

Calculating pH:

Straight after preparation, the pH of the improved formulation (F7) was monitored using a calibrated digital pH metre. The formulations had pH values between 6.7±0.43 to 7.15±0.90. The intended pH range was 6.7-9.4, and all of the formulas fell within this range.

Field Emission Scanning Electron Microscopy (FE-SEM):

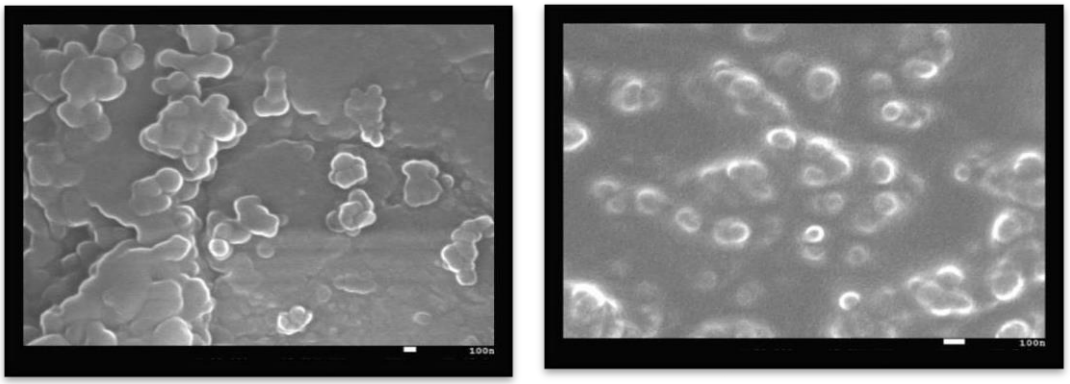

Figure 5: FE Scanning Electron Microscopy

The surface morphology of optimized formulation (F7) examined by FE-SEM was illustrated. The formulation appeared as amorphous particles. When at ×500 magnification, it could be seen that presence of almost spherical structures of nanoparticle.

Viscosity:

One way to describe the difficulty of moving a fluid from one place to another is by its viscosity. When assessing nanosuspensions, viscosity is crucial as it affects how the drug is mixed in a bulk formulation and how the substance flows.

Identifying the viscosity:

Table 2 : Identifying the viscosity

FORMULATION	VISCOSITY
F1	64
F2	67
F3	71
F4	66
F5	69
F6	74
F7	75
F8	63
F9	94

All of the formulations had viscosities between 63 and 94 CPS, and as one moved closer to the results, they showed an increase in viscosity.

In Vitro Study:

Table 3 and figure 6 shows the in vitro release profiles of each formulation. As the concentration of Nepafenac in the formulations was increased which leads to rate of drug release also increased. A higher drug release rate was observed when the concentration of Nepafenac was increased relative to a constant concentration of polymer in the formulation. The formulations F1 to F9 made with drug/Pluronic F127 showed 19.16± 0.79, 28.12±0.67, 39.16± 0.12, 48.18± 0.55, 60.24±0.34, 72.40±0.51, 84.65±0.51, and 95.15±0.21 release in 8 hrs.Respectively.

Table 3: In-Vitro drug release of Nepafenac Nanosuspension

Sr. No.	Time (Hrs.)	% Drug release								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	1	11.14± 0.47	18.87± 0.48	21.80± 0.35	28.36±0 .41	32.60± 0.55	17.69± 0.57	19.16± 0.79	16.86± 0.54	18.03± 0.59
2	2	18.41± 0.50	24.681. 50	32.12± 0.25	35.31±0 .53	34.55± 0.60	20.42± 0.45	28.12± 0.67	19.80± 0.46	23.46± 0.71
3	3	35.14± 0.35	35.18± 0.45	41.12± 0.30	40.32±0 .40	40.41± 0.44	25.51± 0.37	39.16± 0.12	27.07± 041	32.84± 0.38
4	4	48.18± 0.40	48.19± 1.80	56.12± 0.40	52.12±0 .65	51.42± 0.30	31.16± 0.40	48.18± 0.55	39.12± 0.20	42.50± 0.64
5	5	56.18± 0.45	55.12± 0.44	64.17± 0.32	67.70±0 .76	59.12± 0.25	49.14± 0.23	60.24± 0.34	45.20± 0.35	54.18± 0.27
6	6	69.12± 0.55	63.18± 0.33	72.12± 0.23	72.18±0 .56	67.12± 0.46	57.12± 0.34	72.40± 0.51	56.18± 0.25	62.16± 0.32
7	7	74.12± 0.30	72.12± 0.40	79.12± 0.45	79.70±0 .71	75.30± 0.87	68.15± 0.22	84.65± 0.51	68.18± 0.80	69.12± 0.43
8	8	88.80± 0.38	82.12± 0.50	81.12± 0.51	90.15±0 .32	85.16± 0.48	82.25± 0.75	95.15± 0.21	73.15± 0.22	72.15± 0.31

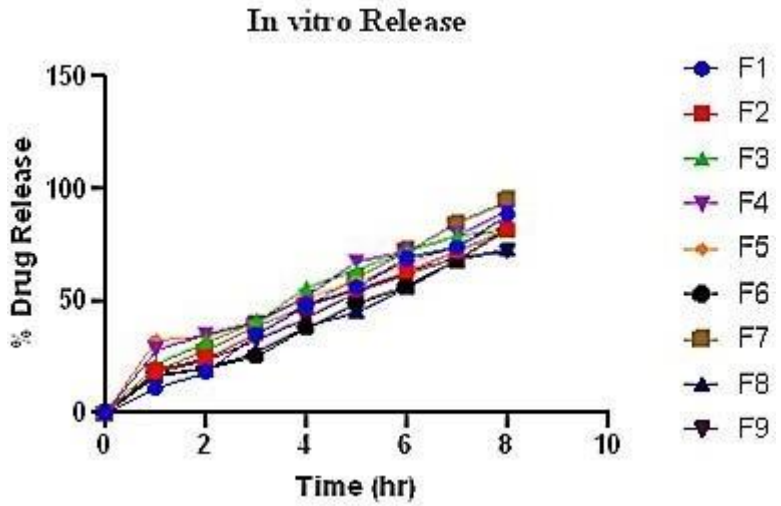

Figure 6: In-Vitro drug release of Nepafenac Nanosuspension

Table 4:Comparison between in-Vitro studyof Optimized batch with marketed formulation

Sr. No.	Time(Hrs.)	F7 Batch	Marketed Formulation
1	1	19.16±0.79	10.20±0.30
2	2	28.12±0.67	15.20±0.67
3	3	39.16±0.12	18.30±0.33
4	4	48.18±0.55	23.30±0.55
5	5	60.24±0.34	29.10±0.21
6	6	72.40±0.51	34.20±0.45
7	7	84.65±0.51	38.20±0.22
8	8	95.11±0.21	41.78±0.34

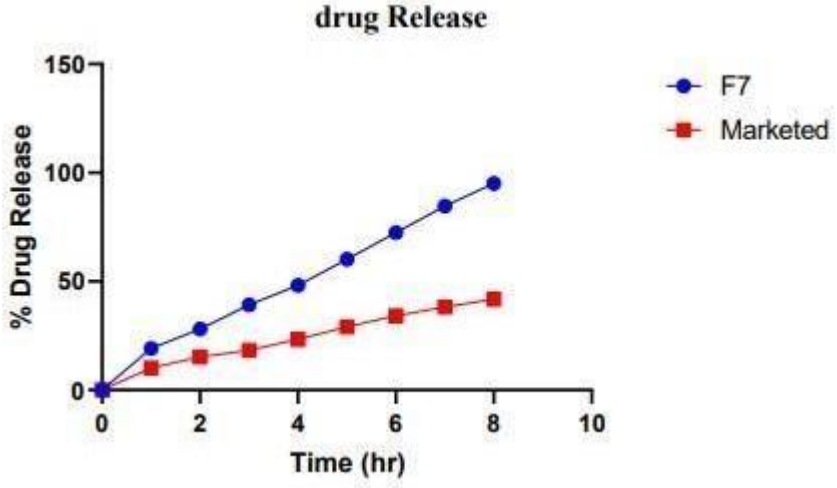

Figure 7: Comparison between in-Vitro study of Optimized batch with marketed formulation

Ex Vivo Study:

The optimised formulation of Nepafenac had a greater corneal permeation (91.12±0.71) after 8 hours in the ex vivo transcorneal permeation assays conducted through an excised goat cornea compared to the commercially available preparation of the same concentration of Nepafenac (45.3±0.59). The ampiphilic nanoparticles had an easier time penetrating the hydrophilic and lipophilic corneal stroma, which may explain why the nanoparticles of Nepafenac were able to increase the drug's penetration.

Table 5: Ex-Vivo Study

Sr. No.	Time (Hrs.)	F7 Batch	Marketed Formulation
1	1	18.13±0.55	12.3±0.32
2	2	26.11±0.67	14.8±0.43
3	3	38.25±0.45	19.7±0.23
4	4	51.45±0.43	24.6±0.44
5	5	62..36±0.32	28.4±0.38
6	6	73.76±0.69	35.2±0.66
7	7	81.23±0.41	40.4±0.43
8	8	91.12±0.71	45.3±0.59

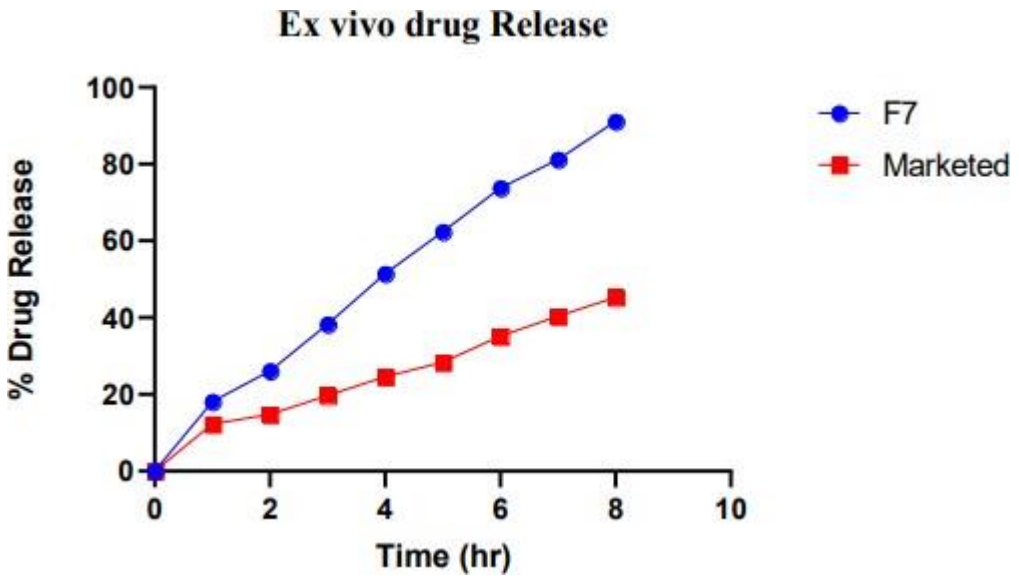

Figure 8: Ex-Vivo Study

Stability Study:-

In analyzing the stability study of optimized formulation (F7) over a period of 8 hours and comparing initial drug release percentages to those after 3 months, several key observations can be made. Initially, drug release percentages showed a consistent increase over time, which is typical for formulations designed for controlled release. After 3 months, there was a slight decrease in drug release percentages across all time points, indicating minor changes in the formulation's release characteristics over time.

This suggests that formulation F7 maintains relatively stable drug release profiles over a 3 month period. The small standard deviations in the data (ranging from ±0.10 to ±0.79) indicate precise measurement consistency, bolstering the reliability of these findings. Factors influencing stability,

such as environmental conditions and formulation components, should be considered when interpreting these results.

Table 6: Stability study of F7 batch

Time (Hrs.)	% Drug Release (Initial)	% Drug Release (After 3 Months)
1	19.16±0.79	18.85±0.75
2	28.12±0.67	27.80±0.65
3	39.16±0.12	38.89±0.10
4	48.18±0.55	47.91±0.50
5	60.24±0.34	59.89±0.30
6	72.40±0.51	71.95±0.48
7	84.65±0.51	84.22±0.47
8	95.15±0.21	94.75±0.18

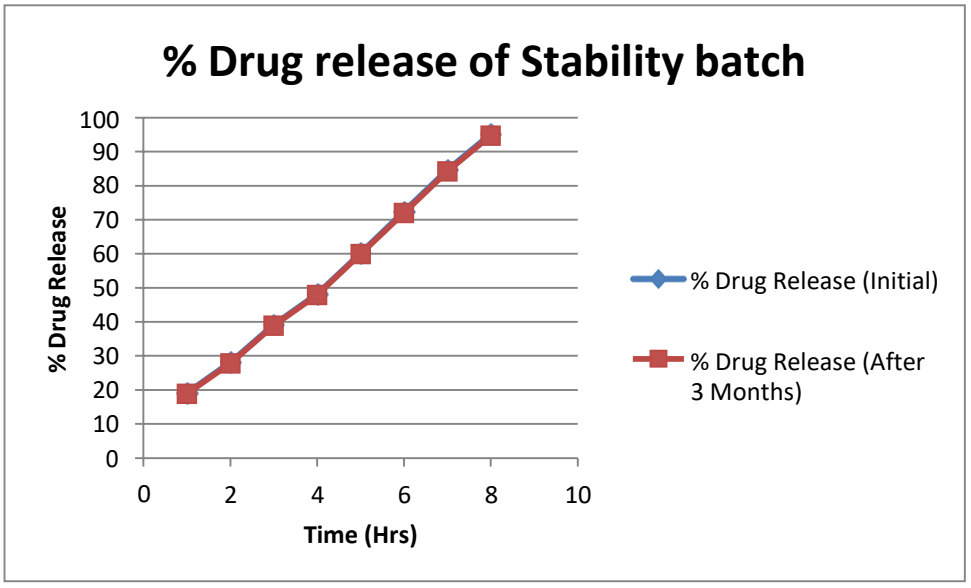

Figure 9: Drug Release of Stability batch

These findings underscore the importance of ongoing stability testing beyond 3 months to assess longer term performance and potential degradation trends. Strategies for enhancing stability should be explored if further optimization is necessary to maintain consistent drug release profiles throughout the product's shelf life.

CONCLUSION:-

The development and evaluation of the Nepafenac nanosuspension shows significant promise in enhancing the bioavailability of poorly soluble drugs, particularly in ocular delivery systems. Utilizing the solvent diffusion method, nanosuspensions were successfully formulated with optimal physicochemical properties, including a desirable particle size distribution and stable zeta potential, crucial for effective drug delivery. In vitro release studies demonstrated sustained and superior drug release profiles over 8 hours compared to conventional formulations, indicating potential for enhanced therapeutic efficacy. Ex vivo transcorneal permeation studies further highlighted its ability to improve drug penetration across the cornea, essential for treating ocular diseases effectively. Stability studies over 3 months confirmed consistent drug release profiles for

formulation F7, affirming its reliability and potential for prolonged shelf life in clinical applications. For future prospective, major focuses on comprehensive preclinical and clinical validations need to be establish the efficacy, safety, and long-term stability of the Nepafenac Nanosuspension. Long term stability assessments under varied storage conditions, alongside toxicity evaluations and pharmacokinetic studies are essential to optimize dosage regimens and ensure patient safety.

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