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Optimization of Felbinac Nanoemulgel - Formulation and Evaluation Employing Advanced Statistical Mixture Design Approach

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Nanoemulgel represents an advanced topical drug delivery system integrating Nanoemulsions and Hydrogels. By blending the stability of nanoscale emulsions with the prolonged release of hydrogels, it improves drug penetration and bioavailability. This advancement shows potential for effective and precise pharmaceutical delivery, especially in dermatological contexts. Optimal Mixture design, a statistical method within the experimental design is employed to fine-tune formulations involving multiple components. In the context of Nanoemulsion development, this approach aids in pinpointing the ideal composition that aligns with specific properties by systematically exploring various component combinations facilitating the optimization of Nanoemulgel formulations.

The investigation included the assessment of droplet size, zeta potential, polydispersity index (PDI) and stability studies. Additionally, morphological characterization through SEM revealed encouraging outcomes.

The Felbinac Nanoemulgel showed enhanced drug release up to 93.63 % and a highly significant difference in therapeutic effectiveness (89.43 %) compared to standard formulation (72.45 %) by anti-inflammatory animal model. Data analysis was performed using two-way ANOVA followed by the Bonferroni post hoc test, confirming the efficacy of the Nanoemulgel in reducing inflammation.

1. Introduction

Nanotechnology offers trusted benefits by allowing drug delivery to the targeted zone for a

superior therapeutic effect. The most suitable nano-formulation, titled nano-emulsions composed of nano-scale droplets, allows for improved targeted drug delivery but pragmatically shows problems with thermodynamic stability during shelf life.[1-2] Considering this question, the nano-emulsion can be transformed into a modern formulation called Nanoemulgel, which is a combination of gel and nano-emulsion. Nanoemulgel is an emerging dosage form for both topical and transdermal drug delivery. This combination was also developed to combat the disadvantages of both dosage forms, namely nano-emulsion and gel. This advancement shows potential for effective and precise pharmaceutical delivery, especially in dermatological contexts.[3-5]

Felbinac, an NSAID, is frequently employed as a topical treatment to alleviate musculoskeletal discomfort and inflammation. Its mechanism involves blocking prostaglandin production, which is responsible for triggering inflammation, pain, and fever in the body. Typically administered in gel or cream form. It is commonly prescribed for conditions like muscle strains, sprains, and arthritis. This localized application enables targeted relief without the extensive systemic side effects often associated with oral NSAIDs.[6 – 9]

The objective of this research is to develop and analyze Nanoemulgel formulations of Felbinac by Optimal Mixture Design for potential topical delivery. This approach aims to address the challenge of high surfactant usage which causes toxicity issues so far. Minimizing the concentrations of surfactants is essential to reduce toxicity in formulations. The selection of versatile surfactants or synergistic blends aids in alleviating adverse effects, simplifying formulations to enhance effectiveness while minimizing potential safety issues.

The formulation incorporated with Carbopol 980F [10] and Pumulen TR-1 [11] to enhance the stability of the Nanoemulgel. Ultrasonication is utilized to reduce and standardize the size of the Nanoemulgel droplets to the nanometre scale. The outcomes of this study are anticipated to provide valuable insights into the design of delivery systems for Felbinac, potentially improving its bioavailability and therapeutic effectiveness. Through the utilization of statistical analysis, the study aims to assess various parameters related to the formulation and performance of Felbinac Nanoemulgel.

2. MATERIALS AND METHODS:

1. Materials: Felbinac was procured from Dhamtec Pharma and Consultants, Navi Mumbai. Carbopol 980F and Pumulen TR-1 were generously provided as gift samples by Lubrizol Advanced Materials India Pvt. Ltd. Transcutol P was gifted by Gattefosse India Pvt. Ltd. Excipients such as Tween 80, Span 20, Menthol, Triethanolamine, Paridol P (Propyl Paraben) and Paridol M (Methyl Paraben) were contributed by IMCD Pvt Ltd, Dadar.

2. Methods:

2.1 Screening of Components:

The formulation of a nanoemulsion involves a delicate balance of surfactants, cosurfactants, and oils to achieve optimal solubility of the drug. By pairing surfactants and cosurfactants in ratios and varying the proportions of surfactant, cosurfactant and oil from 1:9 to 9:1, a range of formulations was explored by using Aqueous titration method.[12] Pseudo-ternary phase

diagrams were generated for different combinations of all components.[13]

2.2 Optimization of Nanoemulsion:

The objective of this study was to optimize the ratio of three components using an I Optimal Mixture Design approach.[14 - 16] With three factors (% Oil, % Water and % Surf: Cosurf blend) under consideration, the design aims to systematically explore the interactions between these components to achieve the desired outcome. A total of 11 runs are planned, each representing a specific combination of the components within the mixture. By varying the proportions of the components across these runs, the design enables a comprehensive assessment of how different ratios impact the overall response as shown in Table 1. Through rigorous analysis of the experimental data generated from these runs as reported in Table 2 while Mixing Time, Mixing Speed and Homogenization Speed process parameters were kept constant, insights can be gained into the most effective ratio of the three components, leading to informed decision-making in formulation optimization.

Table 1: Optimization of the ratio of three components at two levels (High and Low) by using I optimal Mixture Design by keeping real component constant i.e. Drug (Felbinac)

Factors (Variables)		Levels of Factors Studied		
		0 (Low)	+ 1 (High)	Total
A	Oil (Virgin Coconut Oil)	25	39	100 %
B	Water	45	59	
C	Surf: Cosurf Mixture (Tween 80 + Span 80)	15	29	
D	Drug (Real Component - Felbinac)	1		

Table 2: Design Layout for Formulation of Nanoemulsion Batches

Run	Component 1 A: Oil %	Component 2 B: Water %	Component 3 C: Surf: Cosurf %	Component 4 D: Drug %
1	27.25	54.45	17.3	1
2	31.99	45.13	21.88	1
3	29.51	49.76	19.73	1
4	25	59	15	1
5	28.52	45	25.48	1
6	31.94	52.06	15	1
7	25	48.55	25.45	1
8	39	45	15	1
9	25	45	29	1
10	34.25	47.37	17.38	1
11	25	52.05	21.95	1

2.2.1 Formulation of Nanoemulsion:

Following the design layout generated by the I Optimal Mixture Design [17] by using Design Expert® Version 13 Software, Stat ease. all components were weighed accordingly. The surfactants and co-surfactant were combined to form the S_{mix} and the oil phase components were thoroughly mixed while continuously stirring with a homogenizer set at 2000 - 3000 rpm till it became homogenous.[18 – 19] Subsequently, menthol crystals were introduced into the above mixture. the water phase was introduced into the oil phase while stirring persistently. Ultrasonication by Probe sonicator is then applied to reduce droplet size to the nanoscale, completing the process.[20-21]

2.2.2 Formulation of Gel:

Different amounts of Carbopol 980NF (0.5%, 1% and 1.5%) and Pumulen TR-1(0% and 0.3%) gelling agents were dispersed adequately in a sufficient quantity of deionized water.[22] Methyl and Propyl Paraben were dissolved in 5 ml PG with the aid of heat and mixed with dispersion. Followed by the gradual addition of Triethanolamine drop by drop until a uniform gel consistency was achieved.[23]

2.2.3 Formulation of Nanoemulgel:

6 Batches of Nanoemulgel were created by gradually incorporating the optimized nanoemulsion into the gel base in small portions, aided by a homogenizer. This process ensures thorough mixing and uniform distribution of the nanoemulsion throughout the gel base, resulting in the formation of the Nanoemulgel as shown in Table 3 and Figure 1 depicting a general method of preparation of Nanoemulgel.

Table 3: Formulation of Nanoemulgel

Sr.No.	Ingredient	N1	N2	N3	N4	N5	N6
1.	Felbinac (%)	1	1	1	1	1	1
2.	Virgin Coconut Oil (%)	25	25	25	25	25	25
3.	S mix (%)	25.45	25.45	25.45	25.45	25.45	25.45
4.	Carbapol 980 NF (%)	0.5	0.5	1	1	1.5	1.5
5.	Pumulen TR – 1 (%)	-	0.3	-	0.3	-	0.3
6.	Menthol (%)	1	1	1	1	1	1
7.	Propylene glycol	5	5	5	5	5	5
8.	Methylparaben (gm)	0.18	0.18	0.18	0.18	0.18	0.18
9.	Propylparaben (gm)	0.02	0.02	0.02	0.02	0.02	0.02
10.	Triethanolamine	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
11.	Water (q.s)	100	100	100	100	100	100

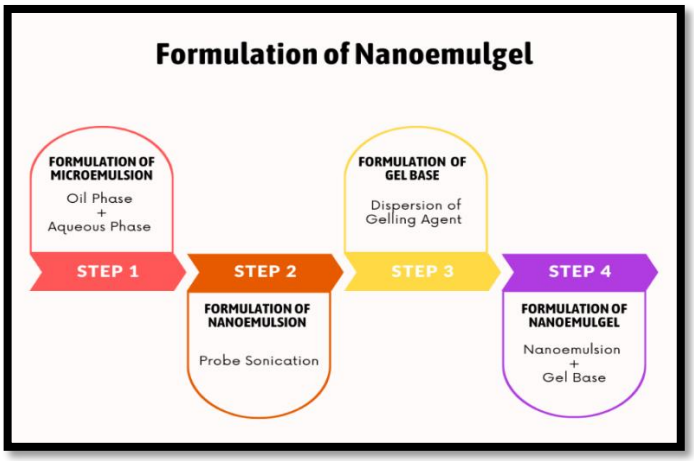

Figure 1: Formulation of Nanoemulgel

2.3 Evaluation Tests of Nanoemulsion:

The evaluation of nanoemulsions involved a systematic assessment of their physical parameters, including appearance, phase separation, and homogeneity, followed by a dilution test. Thermodynamic stability studies, such as heating-cooling cycles, freeze-thaw cycles, and centrifugation tests, were conducted to ensure formulation robustness.[24] Key measurements included droplet size, zeta potential and polydispersity index (PDI) to assess stability and uniformity. Drug content was determined to evaluate the efficiency of encapsulation, while viscosity and pH were analysed to confirm formulation suitability.[25]

2.4 Evaluation Tests for Nanoemulgel:

2.4.1 Determination of Physical Parameters:

Colour an essential parameter was evaluated to ensure uniformity and acceptability. Phase separation was closely monitored to ensure product quality which indicates instability. Grittiness could affect the sensory experience thus evaluated. Lastly, homogeneity was assessed to ensure a uniform distribution of components throughout the Nanoemulgel formulation.[26]

2.4.2 Determination of pH:

The pH of the Nanoemulgel was determined using a digital pH meter. To perform the measurement, 2.0 g of Nanoemulgel was dissolved in 25 mL of deionized water. The pH electrode was then submerged into the dissolved Nanoemulgel solution.[27]

2.4.3 Determination of % Drug Content:

The formulations were diluted in methanol (100 µL of sample diluted 1000-fold). The quantification of Felbinac content was carried out using a UV-visible spectrophotometer at 254 nm.[27]

2.4.4 Determination of Viscosity, Spreadability and Extrudability:

Viscosity measurements were conducted using a Brookfield viscometer equipped with spindle

no.00, with the temperature maintained at 25 ± 0.5 °C. The spreadability of the Nanoemulgel was assessed by placing 1.0 g of the Nanoemulgel in the centre of a glass slide marked with 1 cm^2 grids. Another glass slide was then placed on top of it, followed by the application of a nearly 100 g weight. The spreading coefficient was determined by measuring the area covered by the Nanoemulgel on the slide as a function of time.[27]

2.4.5 Determination of Droplet size and PDI:

Droplet Size and PDI of Nanoemulgel were measured by HORIBA SZ-100 nanopartica by dynamic light scattering technique at 25°C.[28]

2.4.6 Morphological Study of Nanoemulgel:

The surface morphology of the optimized batch was determined by Scanning Electron Microscope at Diya Labs in Mumbai.[28]

2.5 % Drug Release of Plain Drug, Standard Formulation, Nanoemulsion and Nanoemulgel:

In-vitro drug release studies were performed by using Franz diffusion cells. Plain Drug, Std Formulation, Prepared Nanoemulsion and Nanoemulgel (1 g) were eventually applied onto the surface of the cellophane membrane.[29] The receptor compartment was filled with pH 7.4 phosphate buffer solution. The receptor compartment solution was stirred constantly with a magnetic bead maintaining the temperature at 25°C.[30] The aliquot number of samples was (1 ml) withdrawn conservatively from 0 to 12 hrs intervals. The various samples of each time interval were analysed.

2.6 Kinetic Modelling:

Kinetic modelling was used to analyze the drug release behaviours from the Nanoemulgel formulation. Different mathematical models including zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell models were applied to the release data. The model with the highest correlation coefficient (R2) was selected to describe the drug release mechanism and kinetics from the Nanoemulgel.[31]

2.8 Anti-inflammatory Activity Study:

Under the approval of the Animal Ethical Committee [1036/PO/Re/S/2007/CPCSEA/IAEC/20-21/I-3], the anti-inflammatory activity of the prepared Nanoemulgel was evaluated. Three groups of Wistar rats, each containing 6 rats with an average weight of 200 g were selected for the study.

Edema induction will be on the hind paws of rats by using the subplantar injection of 1% w/v carrageenan.[32] The first group served as the control group, the second group of animals was treated with the optimized dose of the Nanoemulgel formulation (1 g), while the third group was treated with the standard Formulation (1 g). Paw volume was measured using a plethysmometer at 0 to 8 hours intervals.[33] The percentage inhibition of edema was calculated in comparison to the control group. Two-way ANOVA followed by the Bonferroni post hoc test was used to analyze the data using GraphPad Prism 5.

2.9 Skin irritation study:

The study protocol received approval from the Institutional Animal Ethics Committee. Three

groups of male Wistar-strain rats (n = 3, weight 180–200 g) were used. The groups included a positive control (0.8% (v/v) aqueous formalin solution as a standard irritant), a Nanoemulgel treatment, and a negative control (no application). Each treatment was applied to a 2 cm^2 area of properly shaven dorsal skin. After 24 hours, the formulations were removed, and the skin was examined for signs of erythema and edema. Any undesirable skin changes, such as alterations in colour and morphology, were visually assessed over a 24-hour period. The reactions were compared and scored against the control group.[34]

3. RESULT AND DISCUSSION:

Solubility of the drug in different surfactants and cosurfactants is crucial, as it directly impacts the efficacy and stability of the Nanoemulsion. From the generated Pseudo ternary phase diagrams, Tween 80 + Span 80 (Blend): Transcutol P (1:1) ratio of Surf: Cosurf finalized for further studies.

As the concentration of the co-surfactant increases, the phase behaviours of the system become more restricted, narrowing the design space. Utilizing surfactant blends provides enhanced control over the formulation process, leading to nanoemulsions that exhibit improved stability, the solubility of hydrophobic drugs and encapsulation efficiency compared to those formulated with single surfactants. Nanoemulsions are commonly created by combining heating and ultrasonication techniques, heating serves to reduce the viscosity of the oil phase, aiding its seamless integration with the water phase. Meanwhile, ultrasonication being a high-energy method is pivotal in breaking down larger droplets into smaller ones. This dual approach results in a nanoemulsion that not only exhibits enhanced properties but also greater stability.

I Optimal Mixture Design allows for efficient exploration of the experimental space, facilitating the identification of the optimal combination that maximizes the desired outcome while considering constraints and interactions between the components.

Response surface analysis revealed the complex relationships between formulation variables and responses, guiding the identification of regions of optimal performance.

Scatter plot compares predicted versus actual droplet sizes, with points coloured from blue (smallest droplet size of 219.46 nm) to red (largest droplet size of 514.76 nm). Overall, the plot suggests the model generally predicts droplet sizes well.as shown in Figure The ternary plot showed how different ratios of these components affected the droplet size of the emulsion, as shown in Figure. The minimum droplet size (219.46 nm) is found at the specific combination of A=25, B=48.6, and C=25.4 as shown in Figure 2.

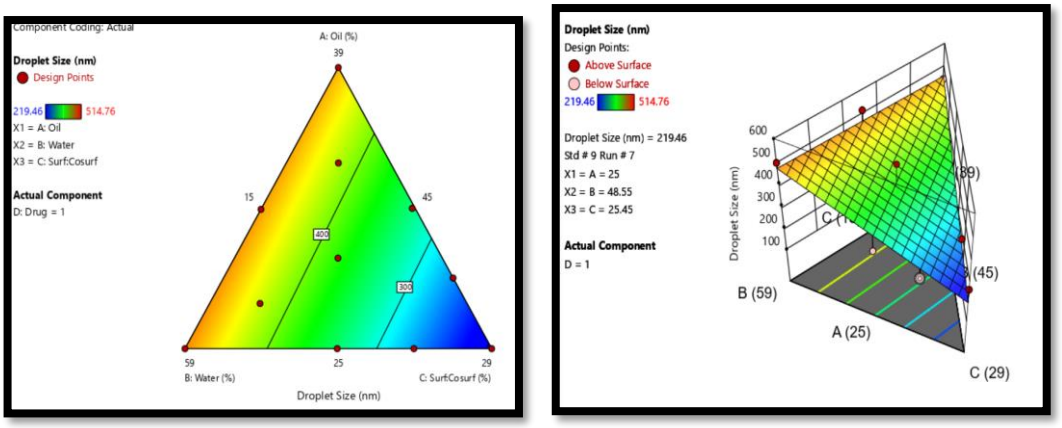

Figure 2: Contour Plot and 3D Response Plot for Nanoemulsion System by Design Expert

The results of the evaluation tests demonstrated that the nanoemulsion exhibited a clear and homogeneous appearance with no signs of phase separation, confirming their physical stability. Thermodynamic stability studies, including the heating-cooling and freeze-thaw cycles, showed no significant changes in the formulations, indicating robustness under stress conditions. The droplet size, zeta potential, and PDI values were within acceptable ranges, suggesting good stability, uniformity, and minimal aggregation. Drug content analysis confirmed efficient encapsulation, while viscosity and pH measurements were consistent with the desired formulation properties. These findings validate the formulation's stability, efficacy, and suitability for intended applications.

Table 3: Physical Parameters and Stability Studies of Nanoemulsion

Sr. No.	Formulation code	Appearance	Phase separation	Dilution Test	Homogeneity	Heating Cooling Cycle	Centrifugation Test	Freeze Thaw Cycle
1	F1	Translucent	None	Stable	Homogenous	Stable	Stable	Stable
2	F2	Translucent	None	Stable	Homogeneous	Stable	Stable	Stable
3	F3	Cloudy	None	Stable	Homogeneous	Unstable	Unstable	Unstable
4	F4	Cloudy	None	Stable	Homogeneous	Unstable	Unstable	Unstable
5	F5	Translucent	None	Stable	Homogeneous	Stable	Stable	Stable
6	F6	Cloudy	None	Stable	Homogeneous	Unstable	Unstable	Unstable
7	F7	Transparent	None	Stable	Homogeneous	Stable	Stable	Stable
8	F8	Cloudy	None	Stable	Homogeneous	Unstable	Unstable	Unstable
9	F9	Translucent	None	Stable	Homogeneous	Stable	Stable	Stable
10	F10	Cloudy	None	Stable	Homogeneous	Unstable	Unstable	Unstable
11	F11	Translucent	None	Stable	Homogeneous	Stable	Stable	Stable

Table 4: Particle Size, % Drug Content, pH and PDI

Particle Size (nm)	% Drug Content	pH	PDI
396.41	91.13	6.52	0.698
281.46	92.17	6.18	0.674
454.23	89.56	6.56	1.101
498.65	80.34	6.43	1.124
281.02	93.14	5.84	0.526
514.76	88.16	6.41	1.232
219.46	97.25	6.52	0.431
452.11	90.05	5.58	1.079
258.73	95.07	6.48	0.464
401.23	90.98	6.45	1.026
262.21	94.88	6.38	0.472

Carbopol 980NF is used as it is a non-benzene polymer. This makes Carbopol 980NF a safer choice in this formulation. Indeed, Pemulen™ TR-1 is used in formulations to help maintain particle size throughout the product's shelf life. It works by forming an adsorbed gel layer around each oil droplet, which generates a physical repulsive force that helps prevent droplets from coalescing.

In nanoemulsions, determining droplet size was essential for assessing stability and drug delivery efficiency, as smaller droplets provided a larger surface area. Zeta potential was a key indicator of emulsion stability; higher values suggested strong electrostatic repulsion that could prevent droplet coalescence. The polydispersity index (PDI) measured the uniformity of droplet sizes, with lower values indicating a homogeneous distribution that was crucial for consistent therapeutic effects and long-term stability of the formulation.

Evaluation of colour, phase separation, grittiness and homogeneity are critical steps in ensuring the quality and acceptability of Nanoemulgel formulations. Each of these parameters plays a significant role in the overall user experience and product performance. By closely monitoring these quality attributes during formulation development, enhance product stability, efficacy, and consumer satisfaction. Continuous improvement and optimization of these parameters are essential to meet regulatory standards and consumer expectations.

The pH influences the chemical and physical properties of the formulation, affects the release and bioavailability of active ingredients, and determines the compatibility with the skin.

Accurate drug content determination ensures that each batch of Nanoemulgel is consistent in its formulation. This consistency is vital for reproducibility of the product's efficacy and safety across different batches. This is essential for delivering the intended therapeutic effect.

Viscosity ensures the stability and appropriate drug release from the Nanoemulgel. Spreadability affects the ease of application, coverage, and ultimately the efficacy. Extrudability influences the ease of dispensing and the user's ability to obtain the correct dose.

Together, these parameters are critical for ensuring that the Nanoemulgel is effective, user-friendly, and stable, ultimately leading to better patient outcomes and product acceptance.

Smaller droplet size ensures a larger surface area for drug release, enhancing bioavailability. A low PDI indicates uniform droplet distribution, which is key to maintaining stability and preventing phase separation. Together, these parameters ensure consistent therapeutic performance and product quality.

A morphological study of Nanoemulgel is significant for understanding the physical structure and distribution of droplets within the gel matrix. It helps in confirming the uniformity and consistency of the emulsion, which is crucial for stability and effective drug delivery.

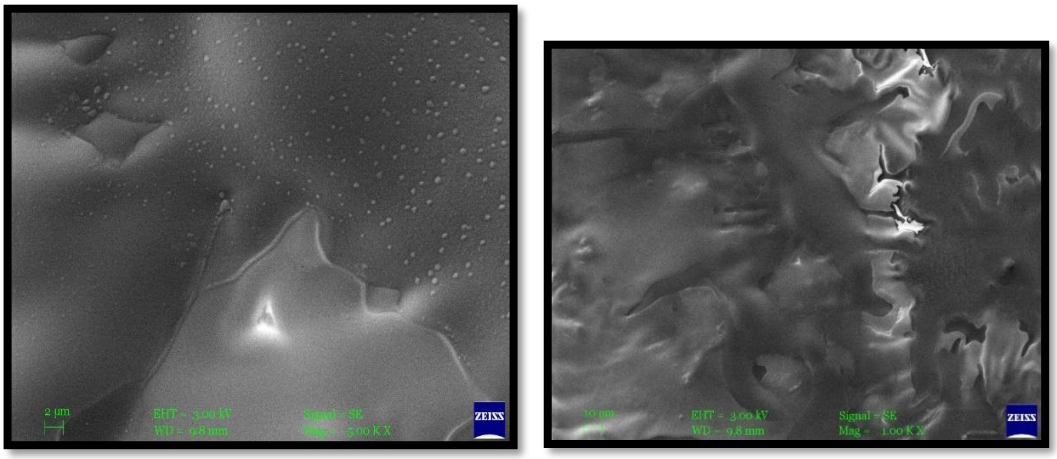

Figure 3: Nanoemulgel loaded with Pemulen TR1 showed homogeneous distribution of Nanodroplets in gel matrix as compared to without Pemulen TR1

This study also aids in optimizing the formulation by revealing any structural anomalies that could affect the gel's performance, ensuring better therapeutic efficacy and quality control.

Comparing the % drug release of Plain drug (18.79%), Nanoemulsion (69.19%) and Nanoemulgel (93.63%). This comparison highlights the enhanced bioavailability and controlled release properties of nanoemulsions and Nanoemulgel over plain drug and Nanoemulsion formulation.

The drug release data were best fitted to the Higuchi model, indicating a diffusion-controlled release mechanism. The linearity of the Higuchi plot suggests that the drug release from the formulation primarily occurred through diffusion from the matrix depicted in Figure 4.

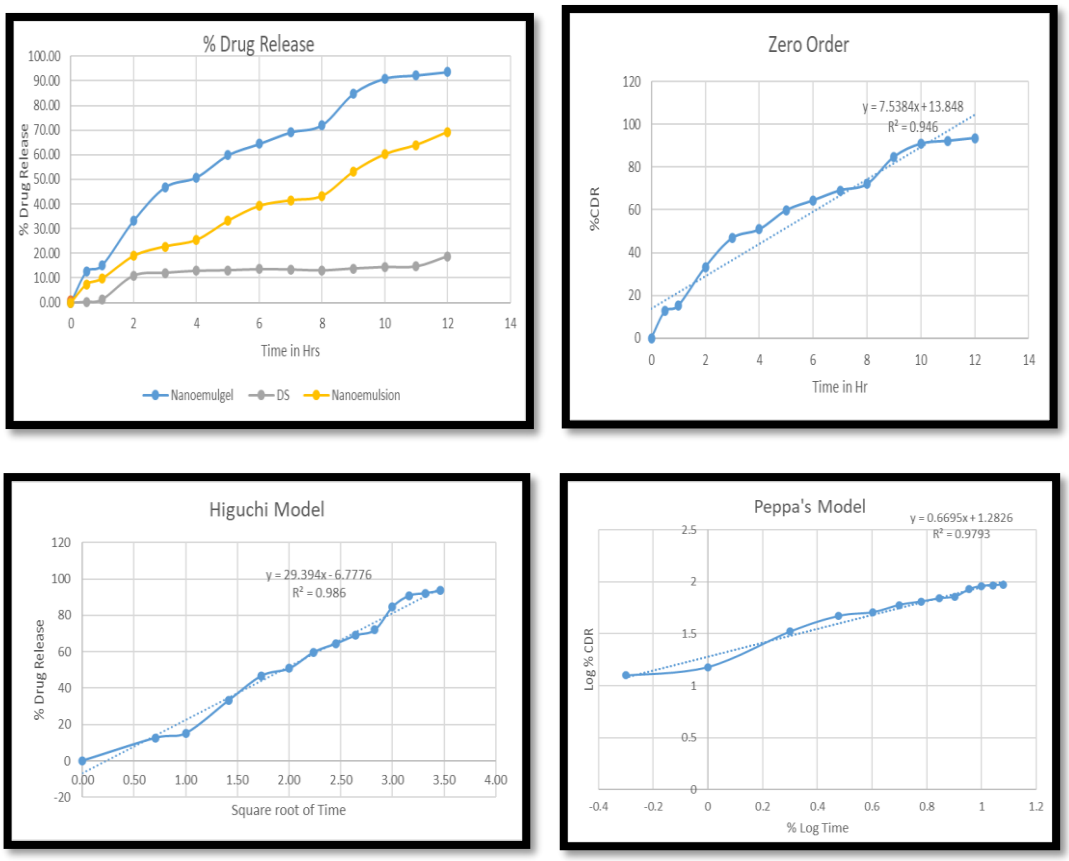

Figure 4: Drug Release and Kinetic Modelling

The Table 5 presents the % inhibition of edema caused by two different Standard group and Nanoemulgel group over time. The data shows that both substances effectively reduce edema, with Nanoemulgel consistently exhibiting higher inhibition rates than Standard at each time point. The most significant inhibition for both substances observed after 8 hours, with Nanoemulgel reaching an impressive 89.43% inhibition as shown in Figure 5.

Table 5: % Inhibition Edema

Time (Hrs)	% Inhibition Edema (Std)	% Inhibition of Edema (NE1)
2	10.33	32.64
4	51.34	72.62
6	68.24	81.65
8	72.45	89.43

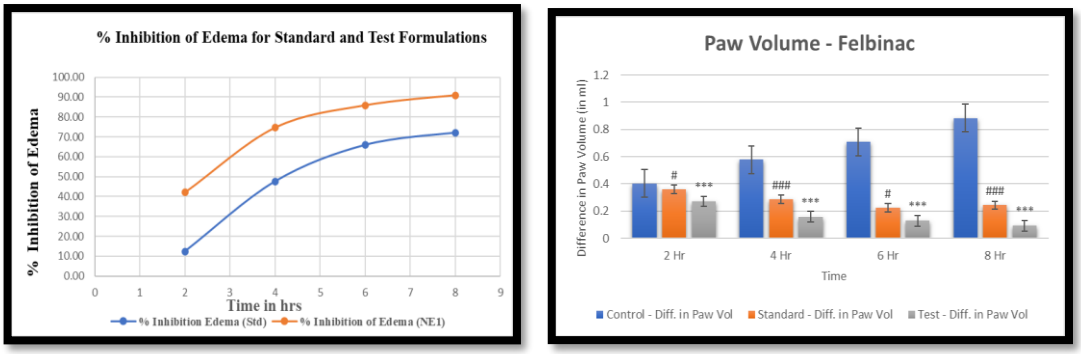

Figure 5: n=6, The difference in paw volume for each group was calculated by comparing it with the control group. Values indicate mean ± S.E.M. (Two ANOVA test followed by Bonferroni post-test). Significance variance against control denoted by *** and Standard - Diff. in Paw Vol vs Test - Diff. in Paw Vol denoted by ### & #. P-Value = P<0.001 & P-Value = P<0.0

The skin irritation study showed that the Nanoemulgel was safe for dermal application. The positive control group (formalin-treated) exhibited significant erythema and edema, confirming its irritant effect. The Nanoemulgel-treated group showed no signs of erythema, edema, or skin changes, like the negative control group. Comparative scoring revealed that the Nanoemulgel irritation levels were negligible and aligned with the non-treated control. These results confirm the Nanoemulgel excellent skin compatibility and non-irritant nature.

4. CONCLUSION:

a stable and efficient Nanoemulgel formulation was developed using a blend of Tween 80 and Span 80 as surfactant and Transcutol P as cosurfactant. The nanoemulsion exhibited good physical stability and high drug entrapment. Carbopol 980NF was used as a thickener for the Nanoemulgel as non-benzene polymer, which further improved stability and user experience. Pemulen TR-1, incorporated into the formulation, effectively stabilized droplet size, ensuring product efficacy and longevity. The in vitro studies demonstrated enhanced drug permeation and Suppression of edema in animals showed improved bioavailability compared to the standard formulation. This Nanoemulgel formulation has promising potential for topical drug delivery.

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