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Formulation and Development of Naproxen Transethosomal Gel for its In-Vitro Anti-Inflammatory Activity

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ABSTRACT:

Background: When taken orally, naproxen, a common nonsteroidal anti-inflammatory medicine (NSAID), is known to cause gastrointestinal adverse effects. Transethosomal formulations were created for transdermal administration in order to reduce these side effects and enhance therapeutic efficacy. **Method of Preparation:** The cold method was used to prepare transethosomes loaded with naproxen. To put it briefly, ethanol was used to dissolve naproxen, phospholipids, and surfactant, and the mixture was then stirred at room temperature. To create transethosomal vesicles, an aqueous phase was subsequently introduced dropwise while being constantly stirred. The resultant dispersion was sonicated to reduce vesicle size and increase homogeneity. **Evaluation:** Particle size, zeta potential, polydispersity index (PDI), and in vitro drug release were all assessed for the formulations. BBD Optimization: To optimize formulation parameters, Box-Behnken Design (BBD) was applied. The physicochemical characteristics were shown to be considerably influenced by the lipid content, surfactant ratio, and ethanol concentration. **Results:** The optimized Naproxen-loaded transethosomal gel (Formulation F2) exhibited a particle size of 176.3 nm, PDI of 0.414, and zeta potential of -20.1 mV, indicating good stability and uniformity. The gel showed a pH of 6.0, spreadability of 6.3 cm, and viscosity of 9940 cP, with a white, semi-transparent appearance. The transethosomal formulation also demonstrated significantly higher in vitro anti-inflammatory activity, with 50% inhibition and an absorbance of 3.46, these results confirm F2 as a stable and suitable formulation for effective topical delivery of Naproxen.

Keywords: Transdermal drug delivery, Naproxen, Transethosomes, BBD Optimization, Transethosomal gel.

INTRODUCTION

Transdermal drug delivery systems (TDDS) offer a non-invasive route for systemic drug administration through the skin. They provide several advantages over conventional routes, including avoidance of first-pass metabolism, sustained and controlled drug release, improved patient compliance, and reduced gastrointestinal side effects [1]. However, the skin's outermost layer, the stratum corneum, acts as a significant barrier to drug penetration. To overcome this, advanced Nano carrier systems such as transethosomes have been developed. These vesicular carriers enhance drug permeation by combining the flexibility of ethosomes with the penetration-enhancing effect of edge activators, making them ideal for delivering drugs like naproxen through the skin effectively [2].

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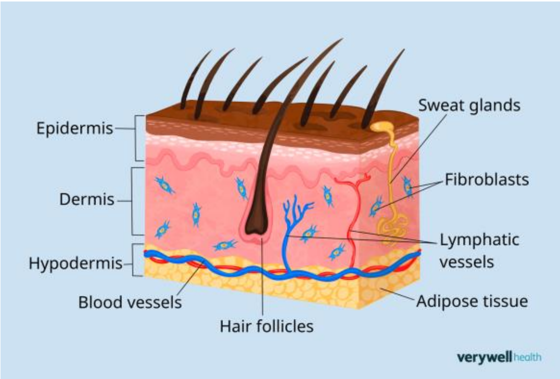


Fig.1: Structure of Skin

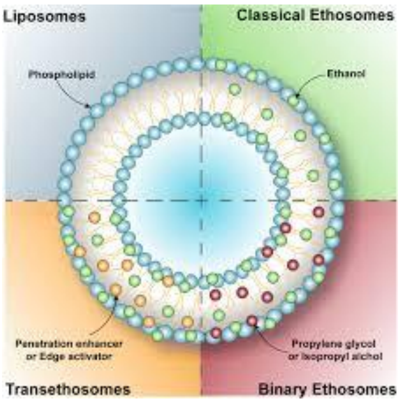


Fig.2: Structure of Transethosomes

Mechanism of action:

Through a synergistic mechanism including their distinct composition of phospholipids, ethanol, and edge activators (surfactants), transethosomes improve transdermal medication delivery. Ethanol has two functions: it increases skin permeability by fluidizing the vesicle bilayer and altering the stratum corneum's lipid structure [3]. Because of the edge activators' ultra-deformability, the vesicles can pass through the skin's tiny intercellular gaps without breaking. Because of their deformability, the vesicles can carry the medication to specific layers of the skin or penetrate deeply. Transethosomes can also combine with skin lipids to promote regulated medication release, which improves drug penetration and deposition.[4] These characteristics work together to make transethosomes extremely effective transdermal drug delivery vehicles that can penetrate the skin's natural barrier while preserving drug stability and efficacy.

Pre-formulation Studies of Naproxen

Table No.1: Organoleptic properties of Naproxen

Colour	White to off white powder
Odour	Practically odourless
Texture	Crystalline powder
Taste	Bitter taste

Melting point:

Fig.3: Melting point of naproxen was found at 147°c

Solubility parameters:

Table No.2: Absorbance of Naproxen drug dilutions

S. No	Concentration	Absorbance
1.	2 µg/ml	0.02
2.	4 µg/ml	0.057
3.	6 µg/ml	0.083
4.	8 µg/ml	0.119
5.	10 µg/ml	0.220

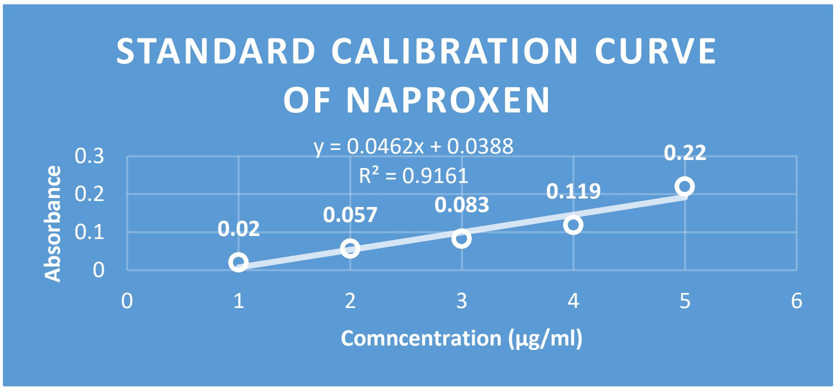


Fig.4: Standard Calibration Curve of Naproxen

Solubility Assessment of Naproxen:

Table No.3: Solubility Assessment of Naproxen

Solvent	Concentration
Phosphate buffer pH 6.8	0.112 ± 0.038
Phosphate buffer pH 7.4	0.108 ± 0.074
Water	0.1 ± 0.065
Ethanol	0.456 ± 0.0447
Methanol	0.856 ± 0.028

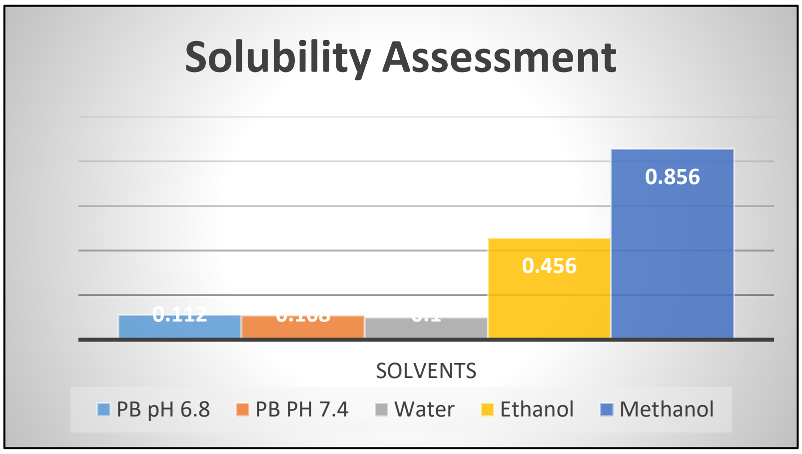
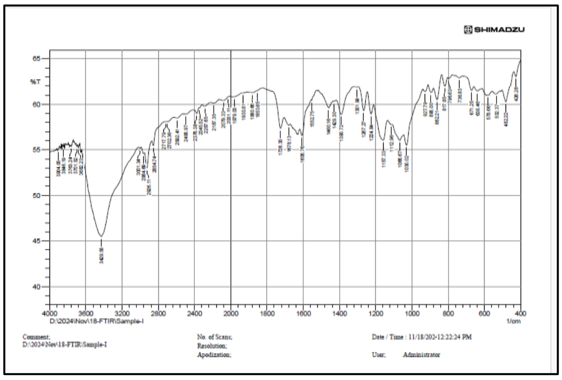


Fig.5: Solubility Assessment of Naproxen

FTIR:



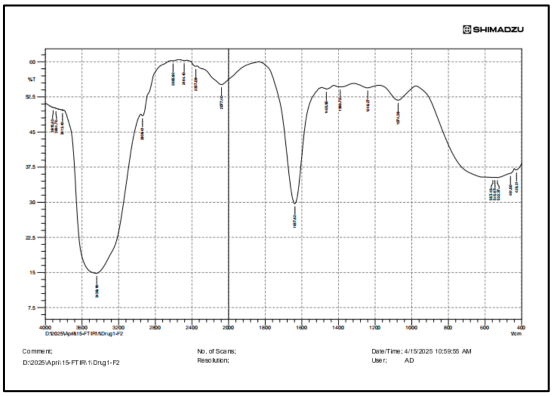


Fig.6: FTIR of Naproxen

Fig.7: FTIR of NPX with Excipient (Carbopol 934)

METHODS AND MATERIALS

Table No.4: Materials and their categories

Ingredients	Category
Lecithin	Phospholipid
Naproxen(GC)	Anti-inflammatory agent
Ethanol	Solvent
Tween 80	Non-ionic surfactant and Emulsifier

Preparation of Transethosomes:

Cold Method

The cold method is a simple and widely used technique for preparing Naproxen transethosomes. Transethosomes are prepared by first dissolving phospholipids (lecithin) and an edge activator such as Tween 80 in ethanol to form the lipid phase. Separately, bi-distilled water is cooled to 4–8 °C to prepare the aqueous phase. Under constant stirring, the lipid phase is gradually added to the cold aqueous phase, prompting the spontaneous formation of transethosomes due to lipid self-assembly in the presence of ethanol and surfactants. Naproxen is then incorporated into the resulting suspension. To ensure uniform vesicle size, the mixture is sonicated using either a bath or probe sonicator. The final transethosomal suspension is stored at 4 °C until further use. [5]

Formulation

Table No.5: Formulation of Naproxen Transethosome suspension

Formulation	Lecithin	Naproxen	Ethanol	Tween 80
NPX 1	4g	200mg	30ml	3ml
NPX 2	4g	200mg	20ml	2ml
NPX 3	2g	200mg	20ml	1ml
NPX 4	6g	200mg	20ml	3ml

Fig.8 Formulation of Naproxen transethosomes

Characterization of Naproxen transethosomes:

Particle size (nm):

One important aspect of transethosomes is particle size, which influences stability, drug release, and skin penetration. Smaller vesicles, usually between 50 and 300 nm, improve cutaneous distribution and absorption. Size is influenced by variables such as lipid content, ethanol, and surfactant type. [6]

Polydispersity Index [PDI]:

It shows that the distribution of particle sizes in transethosomes is uniform. Higher values indicate size fluctuation and possible aggregation, whereas a lower PDI (0.1-1) indicates a more homogeneous and stable formulation. [7]

Zeta Potential:

Zeta potential determines the physical stability of transethosomes by measuring their surface charge. Strong electrostatic repulsion between particles is suggested by higher absolute values (usually > ±30 mV), which lowers the chance of aggregation and increases stability. Typically, methods such as electrophoretic light scattering are used to measure it. [8]

Results:

Particle size

The model selection for predicting particle size considered linear, 2FI, quadratic, and cubic polynomial models. Among these, the quadratic model was suggested as the most suitable, as it provided a better balance of fit without being aliased, despite its overall lack of statistical significance ($p = 0.1806$). The quadratic model showed moderate predictive power, with an Adjusted R^2 of 0.3680 and a Predicted R^2 of 0.3881, which were in reasonable agreement. Although no individual terms were statistically significant at $p < 0.05$, terms such as A^2 ($p = 0.0519$), AB ($p = 0.0576$), and B^2 ($p = 0.0988$) were near-significant, suggesting some potential influence on particle size. The model's Adeq Precision was 4.099, indicating an acceptable signal-to-noise ratio, and the Lack of Fit was not significant ($p = 0.9768$), confirming the model's suitability for representing the data without overfitting. Despite the limitations, the quadratic model can be used to navigate the design space, and further refinement through model reduction may improve its predictive performance.

PDI

For the response variable PDI, several polynomial models were evaluated, with the 2FI and quadratic models being suggested based on sequential model sum of squares. However, none of the models showed statistical significance, and the quadratic model, though not aliased, had a Model F-value of 1.13 with a p-value of 0.4453, indicating that it was not significant relative to noise. Among the model terms, none were statistically significant ($p < 0.05$), though the interaction term AB (Lecithin P-30 and Ethanol) approached significance (p = 0.0649), suggesting a possible interaction effect worth further exploration. The Adjusted R^2 was low (0.0689), while the Predicted R^2 was 0.3269, showing some predictive ability but with limited reliability. The difference between the two R^2 values was acceptable (< 0.2), but the Adeq Precision value of 3.42 was below the desirable threshold of 4, indicating an inadequate signal-to-noise ratio. Despite this, the Lack of Fit was not significant (p = 0.9988), suggesting that the model fits the data reasonably well in terms of residual error. Overall, while the quadratic model may provide some insight, it is not robust enough for reliable design space navigation without further refinement or model reduction.

Results of optimised NPX 2 Formulation

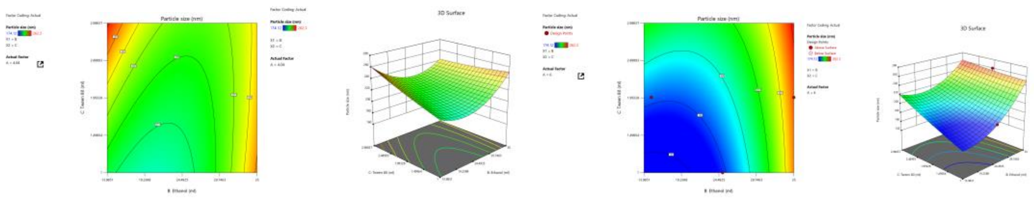


Fig.9: 3D-response graphs representing Particle size of (B) Ethanol and (C) Tween 80

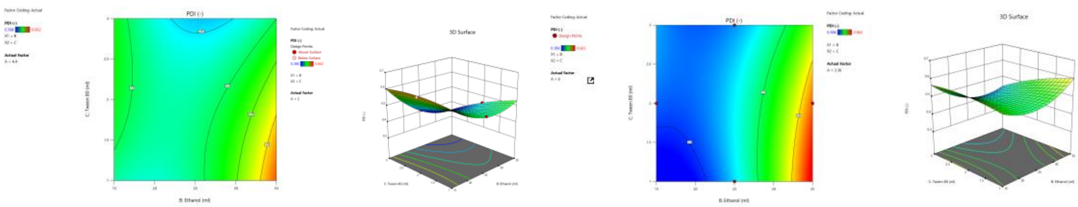
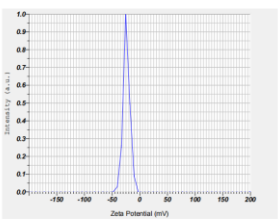


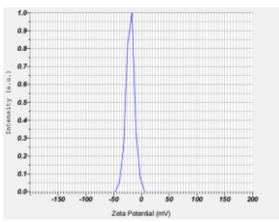
Fig.10: 3D-response graphs representing PDI of (B) Ethanol and (C) Tween 80

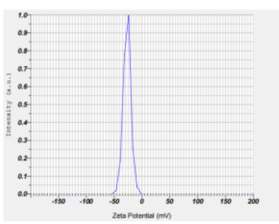
Zeta Potential:

Table No.6: Zeta potential of Naproxen Formulations [NPX]

Formulation	Zeta potential
NPX 1	-23.9mV
NPX 2	-20.1mV
NPX 3	-26.9mV
NPX4	-22.9mV







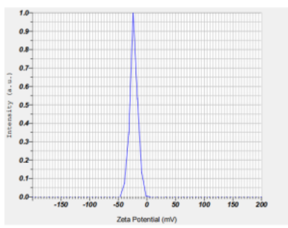


Fig.11: ZP of NPX 1 Fig.12: ZP of NPX 2 Fig.13: ZP of NPX 3 Fig.14: ZP of NPX 4

Transmission Electron Microscopy (TEM)

The high-resolution imaging method known as transmission electron microscopy (TEM) involves passing an electron beam through an extremely thin material. It displays intricate interior structures at the atomic or nanoscale. In biology and materials research, TEM is frequently used to examine features such as nanoparticles, cell organelles, and crystal structures. [9]

For the optimised Formulation NPX 2 TEM is observed

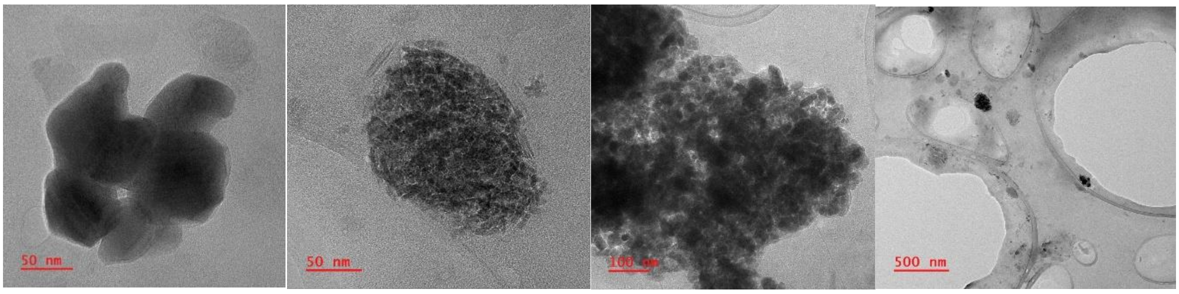
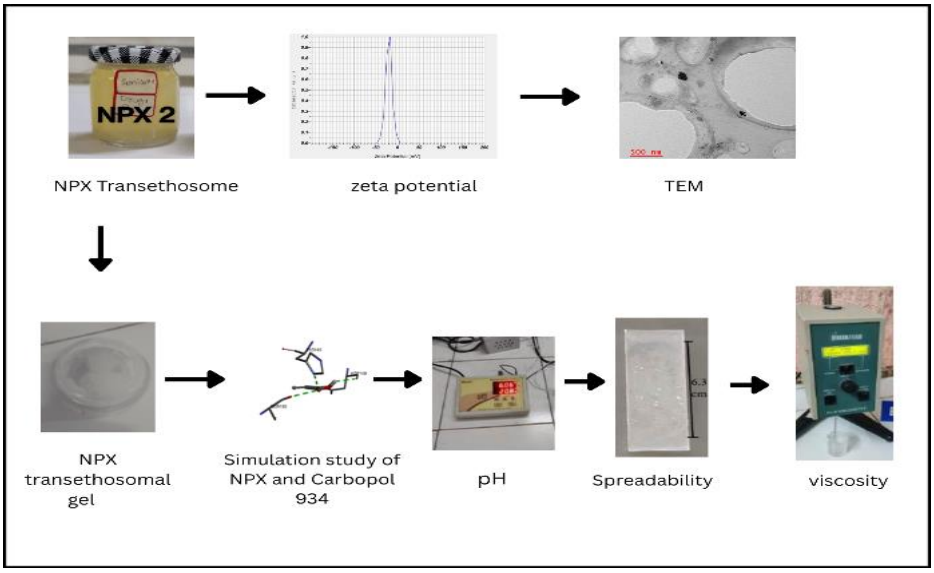


Fig.15: TEM studies of Optimized NPX 2 formulation

Graphical Abstract



PREPARATION OF TRANSETHOSOMAL GEL

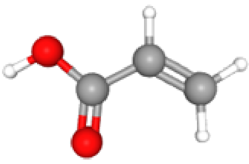
The optimized transethosomal solution is first mixed with an appropriate gelling agent to improve skin retention and application convenience in order to create a transethosomal gel. Carbopol 934, a polymer, 1gm is dissolved in 15ml distilled water and left to fully hydrate, frequently while being gently stirred [10]. Triethanolamine (TEA) is used to adjust the Ph after full swelling in order to create a transparent gel. After that, the optimized Naproxen transethosomal suspension is progressively added to the gel basis while being constantly mixed to guarantee even dispersion without shattering the vesicles [11]. For further analysis, the finished gel is kept at a cold temperature in a covered container. [12]

Excipient Profile:

Carbopol 934

Molecular Weight- 72.06 g/mol

Structure –



Appearance: white, fluffy powder

Category: Polymer

Simulation study of NPX with Carbopol 934

Insilco studies provide valuable resources for scientific research and medication development, allowing computer-based modelling and simulation of biological systems and processes. Although they have many advantages, they should be used in conjunction with experimental procedures for comprehensive research. [13] Molecular docking is most important technique to study protein and ligand binding techniques. In this process we used cb dock 2 free docking website and discovery studio to analyse the amino acids and bonds that are binded [14]. Here the selected protein molecule is obtained in pdfqt format in website Protein Data Bank (RCBS-PDB)[15] and ligands which are selected are extracted from web page PubChem in sdf format, these structures and now further used in CB dock 2 webpage. The structures extracted from the above step are now put in CB dock 2 web page as mentioned and due to auto docking technique it binds the ligand and protein and a combination structure is formed, highest negative vina score possess highest binding capacity, Now the structure complex is downloaded and put in discovery studio, this helps in removing water molecules and find the binding site and type of bond present.[16]

Molecular docking on Naproxen with Carbopol 934

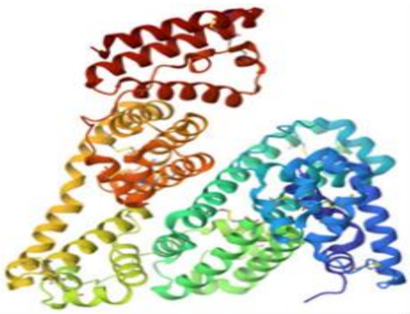


Fig.16: Structure of naproxen

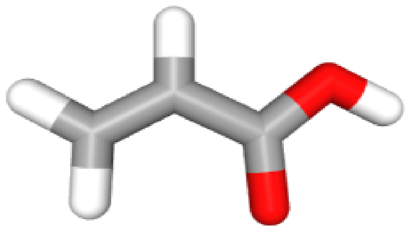


Fig.17: structure of Carbopol 934

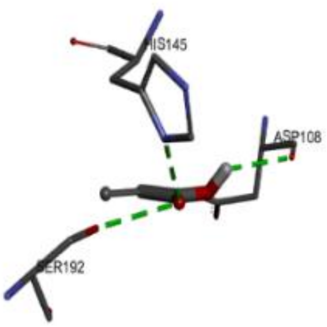


Fig.18: Structure of naproxen with Carbopol 934

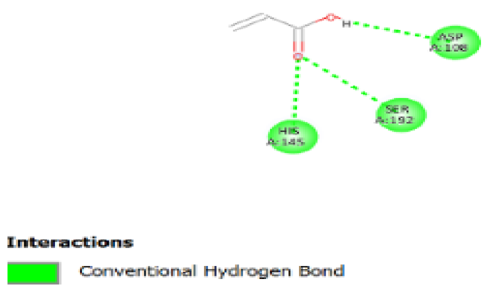


Fig.19: 2d structure of naproxen with Carbopol 934

CurPocket ID	Vina score	Cavity volume (Å^3)	Center (x, y, z)	Docking size (x, y, z)
C5	-3.9	3414	20, 26, 101	28, 24, 31
C1	-3.8	8974	0, 26, 107	35, 35, 27
C2	-3.8	8155	67, 21, 84	35, 35, 29
C3	-3.8	5911	50, 25, 97	35, 31, 31
C4	-3.6	4379	40, 14, 119	31, 35, 25

Fig.20: Binding score of naproxen with Carbopol934

Result:

Molecular docking between naproxen and carbopol 940 with a binding score of -3.9 kcal/mol suggests a moderate interaction, where the two molecules bind with a relatively weak affinity. Naproxen, an NSAID, and carbopol 940, a polymer used in pharmaceutical formulations, may interact in a way that is not particularly strong, but still potentially relevant in some contexts. A binding score of -3.9 indicates a moderate level of affinity, and further analysis would be needed to explore the specific binding interactions and whether this interaction has practical significance for drug formulation or other applications. [17]

Characterization of Naproxen Transethosomal Gel:

Appearance: The gel has a translucent to slightly opaque appearance and is smooth, uniform, and semi-solid. There are no indications of particle debris, grittiness, or phase separation. [18]

Colour: Depending on the gelling agent and transethosomal solution composition, color can range from colorless to pale white. [19]

Consistency: Without being oily or sticky, the formulation's gentle, spreadable texture makes it simple to apply to the skin. [20]

pH: The gel's pH is often adjusted to between 6.0 and 6.5, which makes it appropriate for topical use and compatible with the skin's natural pH [21].

Spreadability: Spreadability affects patient compliance and consistent drug delivery by determining how easily the gel distributes over the skin. Without being very stiff or runny, a transethosomal gel should have good spreadability. The slip and drag method, which uses two glass slides and a predetermined weight to monitor how long it takes for the gel to spread, is frequently used to assess it [22]. Better spreading ability is indicated by greater values of spreadability, which are commonly given in g·cm/s.

Viscosity: Viscosity is a crucial factor that influences the transethosomal gel's stability, spreadability, and drug release. The Naproxen transethosomal gel is perfect for topical treatment since it usually shows pseudoplastic (shear-thinning) behaviour, which means that its viscosity reduces with increasing shear rate.[23] A Brookfield viscometer is frequently used to evaluate viscosity, and depending on the kind and quantity of the gelling agent, appropriate values typically fall between 10,000 and 50,000 cps (Carbopol 934).

In-vitro Anti-inflammatory test: A 5% w/v solution of Albumin (0.45 ml) is added to formulation (0.5g) & Standard (0.5g). Samples are incubated at 37°C for 20 minutes, then heated for 30 minutes at 60°C. After cooling, add 2.5 ml of 6.3 pH buffer. Filter the solution and dilute with the solvent [pH buffer 6.8] and Check in UV spectrophotometer in the range 277nm [24]. Percentage inhibition is calculated using the formula:

$$\%\text{inhibition} = [AS\text{-}1/AC] \times 100$$

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EVALUATION PARAMETERS:

Table No.7: Results of Naproxen transethosomal gel evaluation test

Evaluation test	Result
Appearance	Opaque and transparent
Colour	White
Consistency	Gel consistency
pH	6.0
Spreadability	6.3cm
Viscosity	9940 cps

Anti-inflammatory activity

Table No.8: Results of anti-inflammatory activity

Formulation	Absorbance	%inhibition
Naproxen Topical Gel	1.83	30.7%
Naproxen Transethosomal gel	3.46	50%

Based on the evaluation parameters, the optimized Naproxen-loaded transethosomal gel formulation (Formulation 2) demonstrated favorable physicochemical characteristics suitable for topical application. The formulation exhibited an appearance that was both opaque and transparent with a uniform white color, indicating good homogeneity and aesthetic acceptability. The pH value of 6.0 is within the acceptable range for skin application, suggesting minimal risk of irritation. A spreadability of 6.3 cm indicates ease of application and sufficient coverage on the skin surface. Furthermore, the viscosity of 9940 cps suggests an ideal consistency that ensures good retention on the skin while allowing smooth application. Overall, these results support the suitability of this optimized transethosomal gel for effective and patient-friendly topical delivery of Naproxen.

Fig.21: pH of NPX 2

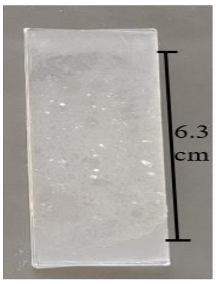

Fig.22: Spreadability of NPX 2

Fig.23: Viscosity of NPX 2

BOX BEHNKEN DESIGN OPTIMIZATION

One kind of response surface methodology (RSM) for process and formulation optimization is Box-Behnken Design. Compared to a full factorial design, it requires fewer experimental runs and is effective for examining the impact of several independent variables (factors) on one or more dependent variables (responses). BBD makes formulas involving sensitive materials safer by generating quadratic models without the use of extreme (corner) points.[25]

Procedure:

Selecting the independent variables (factors) to be examined, usually three or more, is the first stage in the Box–Behnken Design (BBD) optimization process. Each factor is defined at three levels: low (–1), medium (0), and high (+1). The BBD is used to create a design matrix based on these inputs. It carefully arranges the trial runs, avoiding extreme or corner spots, making it safer for formulations that are sensitive.[26]. Intended responses (vesicle size, entrapment efficiency, or zeta potential) are then measured once the formulations have been created in accordance with the design matrix. The link between variables and responses is modeled by fitting the collected data to a second-order polynomial equation. The importance of the model is assessed using statistical analysis, namely ANOVA, which includes p-values, R2, and lack-of-fit.[27]

Table No.9: Factors and Levels

Independent variables	levels		Dependent Variable
	low	High	
Lecithin	2g	6g	Particle Size (nm)
Ethanol	10ml	30ml	Polydispersity Index
Tween 80	1ml	3ml	Zeta Potential

Table No.10: Box Behnken Design Experiment with measured responses

Std	Run	Factor 1 A: Lecithin gm	Factor 2 B: Ethanol ml	Factor 3 C: tween 80 ml	Response 1 Particle size nm	Response 2 PDI
7	1	2	25	3	174.12	0.408
1	2	2	15	2	215.84	0.612
5	3	2	25	1	179.12	0.502
15	4	4	25	2	218.92	0.662
8	5	6	25	3	215.2	0.421
10	6	4	35	1	245.3	0.623
9	7	4	15	1	215.12	0.512
4	8	6	35	2	260.2	0.645
13	9	4	25	2	255.12	0.545
17	10	4	25	2	236.15	0.412
12	11	4	35	3	238.1	0.474
11	12	4	15	3	262.3	0.546
6	13	6	25	1	178.14	0.442
16	14	4	25	2	181.21	0.417
2	15	6	15	2	178.28	0.413
14	16	4	25	2	179.26	0.386
3	17	2	35	2	180.21	0.456

CONCLUSION:

Based on comprehensive characterization and evaluation, Formulation F2 has been identified as the optimized Naproxen-loaded transethosomal gel. Among the tested formulations, F2 exhibited a particle size of 176.3 nm, a polydispersity index (PDI) of 0.414, and a zeta potential of -20.1 mV, indicating a stable, well-dispersed nano-vesicular system with uniform particle distribution—ideal for enhanced skin permeation and formulation stability. Additionally, the gel formulation of F2 demonstrated favourable physicochemical properties for topical application. It appeared both opaque and transparent with a uniform white colour, suggesting good homogeneity and aesthetic appeal. The pH of 6.0 is within the acceptable dermal range, indicating minimal irritation potential. A spreadability of 6.3 cm ensures ease of application and effective skin coverage, while a viscosity of 9940 cps provides adequate consistency for skin retention without compromising spreadability. The transethosomal formulation also demonstrated significantly higher in vitro anti-inflammatory activity, with 50% inhibition and an absorbance of 3.46, overall, these results confirm that F2 is a stable, effective, and user-friendly formulation suitable for the topical delivery of Naproxen.

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