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Improving the Therapeutic Efficacy of Felbinac: A Nano Carrier-Based Transdermal Delivery System

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Nowadays, TDDS is a propitious approach for developing a formulation with enhanced permeation, reduced gastrointestinal side effects, and improved patient compliance. There are several ways to enhance transdermal permeation, in which the incorporation of nano lipid carriers like transferosomes; is observed as an efficient method for the delivery of drug candidates transdermally. Felbinac has promising action in treating severe pain, inflammation, and rheumatoid arthritis. The present study is based on crafting a transferosomal patch of felbinac aiming to enhance transdermal permeation and improve efficacy to get better patient compliance. The transdermal patch is evaluated for different quality attributes. A significant enhancement in drug permeation was observed. This shows a ray of hope towards developing an effective transdermal formulation.
Keywords: Nanolipid carrier, PSA, Transferosome, Transdermal patch, Anti-inflammatory Activity.

1. Introduction

Transdermal drug delivery systems are becoming very popular nowadays because of their superiorities compared to other dosage forms. Such as a non-invasive nature, self-administration can be possible and provides a steady infusion of drugs over a longer time which is suitable for short biological half-lives—avoidance in therapeutic failure, restraint of first-pass metabolism[1], etc. There are different types of transdermal systems are available but among them, drugs in the adhesive type of transdermal patches have more advantages. It contains PSA and serves two purposes at a time; firstly it makes adherence of transdermal patch to the skin by maintaining close contact and promotes drug delivery. And secondly, it allows the drug to diffuse through the skin at a controlled rate. Also, it has a simple and cost-

effective manufacturing process[2]. To improve transdermal drug delivery without causing skin irritation, nanocarrier lipid vesicles are a promising alternative to techniques like iontophoresis, sonophoresis, and electroporation, which can lead to skin irritation[3]. Felbinac is a nonsteroidal anti-inflammatory drug used to treat severe pain and inflammation. Understanding a lipophilic property of felbinac[4], fencing from lipophilic stratum corneum to hydrophilic epidermis may observe vital resistance. Subsequently, a multilamellar nano lipid carrier will be a compelling method to impact log p of felbinac. Nanocarrier vesicles like trnasferosomes are a very effective approach to enhance skin permeation. The combination of phospholipid and edge activators makes it more deformable to penetrate easily into the skin. So the present research work has formulated nano carrier lipid vesicles like transferosomes; loaded into the DIA type of transdermal drug delivery system to enhance its permeation through the skin. And also to improve patient compliance. Transferosomal formulations are screened by 3^2 full factorial design and the selected batch is loaded into transdermal patches optimized by D-Optimal design[5, 6].

2. Material Methods:

Felbinac was procured from Dhamtech Pharma, Mumbai. For Transferosomes, Phospholipid [Soya Phosphatidylcoline] was procured from VAV Lipids, Mumbai. Duro-Tak 87-1625 was procured as a gift sample from Henkel Adhesives, Belgium. The backing membrane Scotchpak 9733 and the release liner Scotchpak 1022 were procured from Alkem Laboratories, Mumbai.
Methods: Preformulation studies have been carried out by studying the physicochemical properties of felbinac. Identification of the drug has been carried out by using IR, NMR, and mass spectroscopy. While compatibility has been carried out by DSC analysis. Transferosomes were prepared using a handshaking method. Phospholipids and Tween 80 were mixed in a round bottom flask (RBF) with the desired drug dose. A solvent mixture of chloroform and ethanol (4:1 ratio) was added and shaken at the lipid transition temperature. After solvent evaporation, a thin lipid film formed. This film was hydrated with phosphate buffer, shaken, and sonicated to obtain vesicles of the desired size[7]. A transferosome-loaded transdermal formulation has been developed by screening a transferosomal formulation first by 3^2 full factorial designs. (Table 1) The selected batch has been loaded into a transdermal patch that has been optimized by D-optimal design (Table 3) to get the final formulation[8, 9].
Based on trial batches, the loading dose and excipients have been finalized. The drug's loading dose has been finalized by determining the formulation's transdermal flux[10]. Flux has been determined by 'Franz Diffusion Cell' using a cellophane membrane.
Flux[11, 12] = (Cumulative amount 2 – Cumulative amount 1) / (T2 – T1) (A), Whereas T- Time point and A- Active Diffusion surface area
After finalizing the loading dose, transferosomes are developed by 3^2 full factorial screening design. (Table 1) in which the ratio of phospholipid and edge activator are considered independent factors while vesicle size and entrapment efficiency are considered s dependent factors, with 3 levels of concentration[13]. The screening was done by using Design Expert 8.0.6.

Sr. No.	Batch	Factor 1 Ratio of Phospholipid: Edge Activator	Factor 2 Sonication Time (Min)
1	T1	1:1	10
2	T2	2:1	10
3	T3	3:1	10
4	T4	1:1	20
5	T5	2:1	20

6	T6	3:1	20
7	T7	1:1	30
8	T8	2:1	30
9	T9	3:1	30

Table 1. Screening of nanocarrier Lipid vesicles by 3^2 full factorial design.

Preparation of Transdermal patch- Optimized transferosomal formulation has been mixed with Duro-Tak, an adhesive polymer with ethyl acetate as a solvent to maintain the desired consistency. Add permeation enhancer oleic acid and mix the solution to achieve the desired consistency. Spread the matrix solution on the backing membrane scotchpak 9723 with the help of a film applicator and keep it for drying. After evaporation of solvent protects the patch from environmental factors with the help of the release liner scotchpak 1022[14]. Based on significant results, the T6 Batch has been selected to load into the transdermal patch as it has shown the lowest vesicle size and highest entrapment efficiency as per the requirement. Again to get accuracy in the results, transdermal formulation has been optimized using a D-optimal design, (Table 2) in which one independent factor such as concentration of adhesive matrix polymer has been selected at two levels and studied their effect on drug release and drug content[15].

Tabel 2 Optimization of Transdermal Formulation by D- Optimal Design

Sr. No.	Batch	Factor 1 Adhesive Polymer Concentration (mg)
1	F1	89.4
2	F2	86.4
3	F3	75
4	F4	95
5	F5	83.4
6	F6	80.5

Evaluation[16, 17]—Transdermal patches have been evaluated for different quality parameters, such as weight, thickness, thumb tack test for adhesion, rolling ball test, moisture content, in-vitro drug release, and drug content.

Drug Release[18]: For the in-vitro diffusion study, the Franz diffusion cell apparatus (Orchid Scientific) has been used. The receiver compartment of the cell is filled with freshly prepared phosphate buffer 7.4, which has having capacity of 20ml. The cellophane membrane was placed carefully between the donor and receiver compartment. Transdermal formulations (F1-F6) with a patch area of $1cm^2$ were carefully placed on the membrane. The amount of drug permeated through the membrane in the receiver compartment is determined by withdrawing 2ml of sample from the receiver compartment with hourly time intervals. And the same amount of fresh phosphate buffer is replaced in the receiver compartment. The withdrawn samples were analyzed by UV spectrophotometer and absorbance was taken at 254nm. The cumulative percent drug release vs. time illustrates the in vitro release study's findings.

Drug content: A patch was cut into a 1cm sq. area and dissolved in a sufficient quantity of methanol solution. The volume was made up to 50 ml, and the prepared solution was shaken for 15-20 min using a mechanical shaker. After shaking, the solution was filtered using Whatman filter paper. The UV absorbance was measured at 254 nm, and the drug content was calculated.

Ex-vivo Permeation studies[19, 20]- Ex-vivo permeation studies for transferosomal patches were determined using the Franz diffusion cell apparatus (Orchid Scientific. The receptor

compartment was the rat's abdominal skin facing the stratum corneum towards the patch. A 20 ml pH 7.4 Phosphate buffer solution was placed in this compartment and maintained at 37 ± 5°C. The patch, acting as the donor compartment with an effective diffusion area of 1cm², was then applied over the skin. The amount of Felbinac released from the patch was measured by collecting 2 ml samples from the receptor compartment at hourly intervals. After each sample was taken, an equal amount of pH 7.4 Phosphate buffer solution was added back to the compartment. The collected samples were then analyzed using UV spectrophotometry at 254 nm to determine the concentration of Felbinac.

3. Result and Discussion

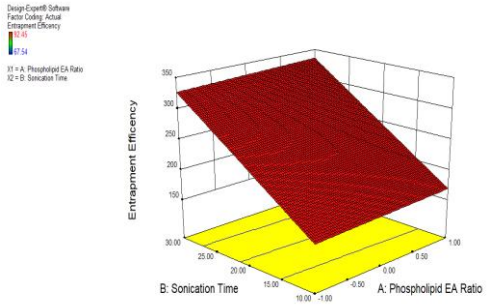
To decide the loading dose transdermal flux has been calculated and compared with targeted flux. The ideal dose of felbinac for the transdermal formulation is about 3-10 %, here to achieve a targeted flux of 25µg/cm^2/hr, 3, 5, and 7% of felbinac have been used and performed diffusion studies by using Franz diffusion cell. Studies have indicated that a 5% felbinac formulation achieves a flux comparable to the target flux, confirming that this concentration is sufficient to maintain sink conditions.

Optimization of Transferosomes -Transfersomal formulation with loading dose 5mg determined by flux calculation has been screened by 3² full factorial design and the T6 batch was selected to load into transdermal patch formulation.

Table 3. 3² full factorial Screening design results for vesicle size and entrapment efficiency

Sr. No.	Batch	Vesicle Size (nm)	Entrapment Efficiency %
1	T1	400.56	67.54
2	T2	396.5	72.02
3	T3	371.6	75.43
4	T4	353.2	80.32
5	T5	300.03	82.32
6	T6	200	92.45
7	T7	290.67	86.42
8	T8	275.5	88.12
9	T9	250.75	90.31

Interpretation of results obtained by 3² full factorial screening design- The statistical technique ANOVA (analysis of variance) is used to evaluate the significance of factors which has been used viz. ratio of phospholipid-surfactant and sonication time on response variables such as vesicle size and entrapment efficiency of transferosomal vesicles. The F value and P value assess the significance of the model. A significant P value of 0.01 (Std. P value ≤ 0.05) indicates that factor A, i.e., the ratio of phospholipid to surfactant, significantly affects the response. Similarly, factor B i.e. sonication time is also assessed, and a significant P value of 0.01 indicates a substantial effect on the response variables.



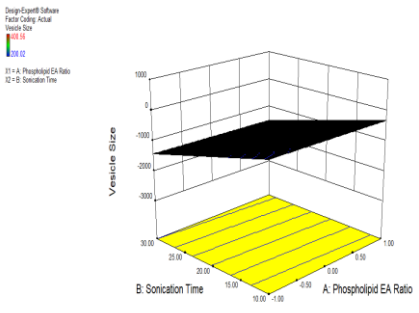
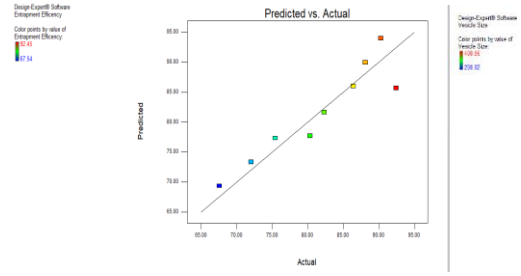


Fig.1 Fig. 2

Fig 1. 3D surface plot for the response 1. Entrapment Efficiency. Fig.2. 3D surface plot for the response 2 vesicle size



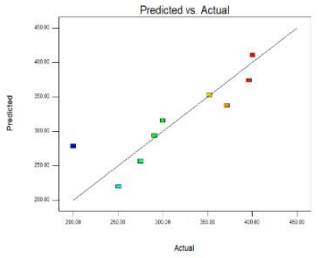


Fig 3. Predicted vs. actual plot for the response Entrapment Efficiency. Fig.4 Predicted vs. actual plot for the response vesicle size.

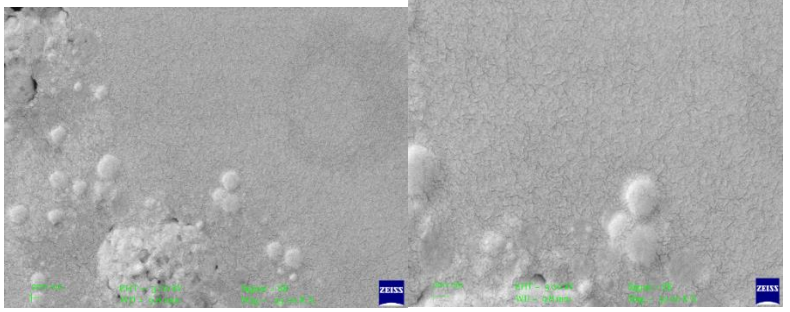
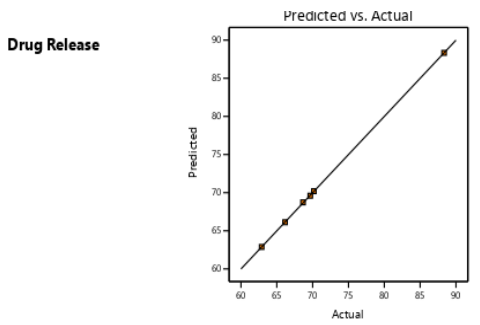


Fig 5. & 6 FESEM images of optimized T6 batch of felbinac transferosomes showing vesicle size around 200 nm.

The 3D surface plots are visual representations of how the entrapment efficiency and sonication time are influenced by independent variables like the ratio of phospholipids to edge activator (Surfactant) and sonication time. (The surface appears to have a single peak, suggesting that there is an optimal combination of Phospholipid EA Ratio and Sonication Time for maximizing Entrapment Efficiency. The slope along the A-axis (Phospholipid EA Ratio) seems to be steeper than the slope along the B-axis (Sonication Time), indicating that changes in Phospholipid EA Ratio have a greater influence on Entrapment Efficiency than changes in Sonication Time.) The transdermal patches have been optimized using a D-optimal design. The final formulation F4 has been selected based on desired drug release and other evaluation parameters for transdermal patch formulation such as weight, thickness, thumb tack test, rolling ball test, etc.

Table 4. D Optimal optimization design results for Drug Release and Drug content.

Sr. No.	Batch	Concentration of Adhesive matrix Polymer	Drug Release (%)	Drug Content (%)
1	F1	89.4	70.16	75.12
2	F2	86.4	69.67	72.5
3	F3	75	62.88	65.2
4	F4	95	90.34	94.12
5	F5	83.4	68.66	68.2
6	F6	80.5	66.15	70



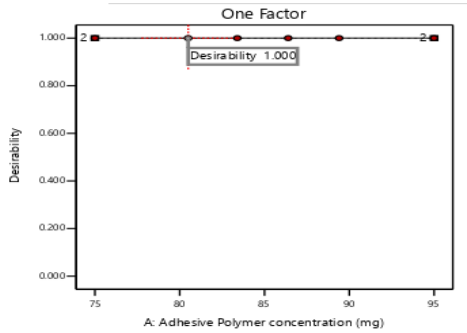


Fig. 7 Predicted Vs Actual values plot Fig. 8 Desirability Plot

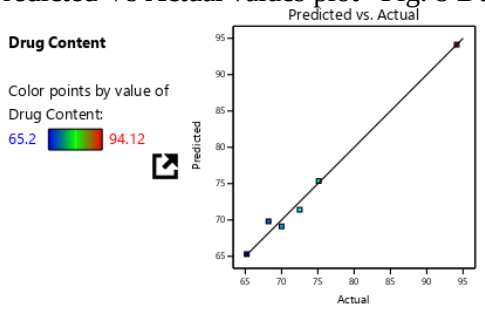


Fig.9 Predicted Vs Actual Values Plot

Interpretation of Results of RSM D Optimal Design- Using this optimization design for transdermal patches, data was analyzed by ANOVA for the quartic and cubic models. In this case, factor A, i.e., concentration of adhesive matrix polymer, has also shown a significant effect on drug release response. (P value 0.009) as well as drug content (P value 0.005). Also, the desirability plot shows how the desirability of response variables changes with adhesive polymer matrix concentration. Also, the graph has suggested an optimal range of concentration of adhesive polymer for achieving the desired drug release and required drug content. (As desirability of 1 indicates the most desirable response for the given factor.) Along with this data for both the responses, the adjusted R^2 (0.9, 0.9) is in reasonable agreement with predicted R^2 (0.8, 0.9), indicating good model and predictive power fitting. Transdermal patches have been evaluated for different quality parameters such as drug release, drug content, weight, thickness, rolling ball test, and tackiness by thumb tack test. As shown in the Fig. 10, batch no. F4 has shown maximum drug release within 12 hrs. Also, it has demonstrated maximum drug content.

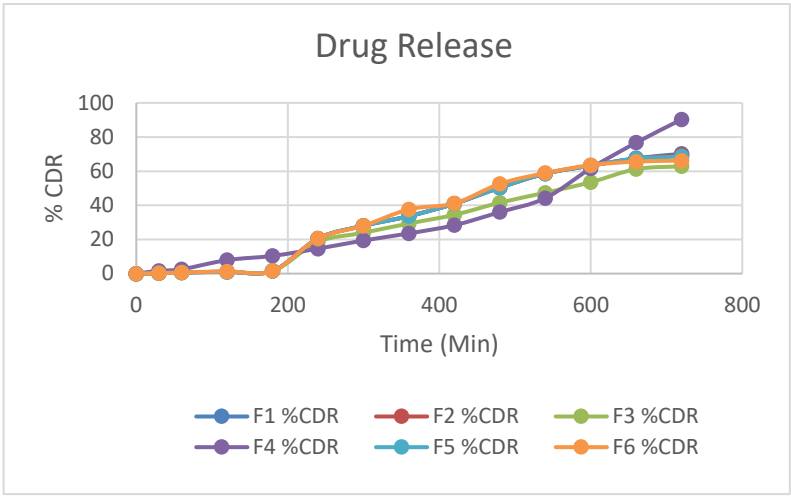


Fig 10. Drug Release of F1 to F6 Batches of Transdermal Patch

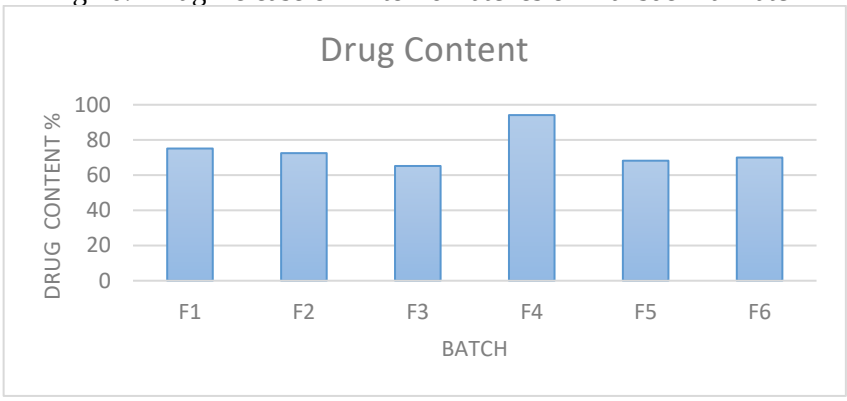


Fig 11. Drug content of F1 –F6 Batches of Transdermal Patch

Table 5. Evaluation of Transdermal patches.

Sr. No.	Batch	Weight (mg)	Thickness	Rolling ball test (cm)	Thumb Tack test	Moisture Content %
1	F1	104.2±2.34	0.62 ±0.01	6	++	1.95±0.002
2	F2	103.4±3.21	0.64 ±0.02	4.2	+	1.87±0.006
3	F3	102.2±2.45	0.65±0.01	8.5	+	0.98±0.010
4	F4	107.3±3.45	0.66±0.01	3.7	+++	0.18±0.034
5	F5	106.4±3.45	0.63±0.03	7.4	++	1.81±0.046
6	F6	105.3±4.52	0.67±0.45	8	+	1.05±0.022

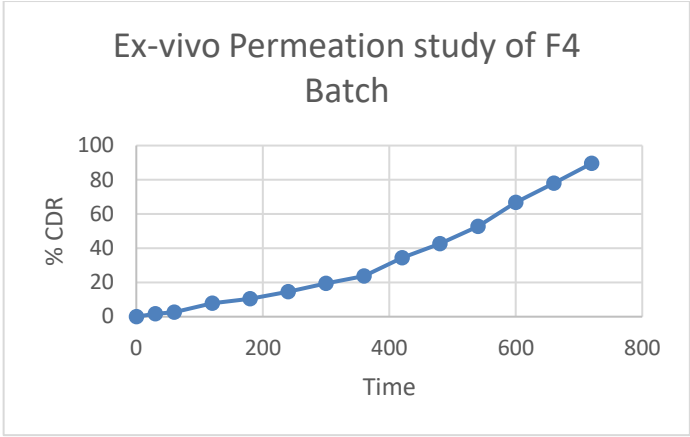


Fig.12 Ex-vivo permeation study for optimized F4 Batch-Permeation studies of Felbinac nanocarrier loaded transdermal patch shows 89.55% drug permeation through rat skin.

Anti-inflammatory Activity[21, 22]- The study measured the swelling of rat paws for 24 hours and calculated the percentage inhibition of swelling. The results were graphically represented, demonstrating a significant decrease in hind paw swelling after applying both the test patch and the standard patch compared to the control group. This indicates that both the test and standard groups were more effective in reducing swelling than the control. The study found that formulation F4 was the most effective in reducing inflammation caused by carrageenan in rats. Table 6 shows the percentage inhibition of edema for both formulations within 12 hours: the standard formulation inhibited 81.45% of edema, while the test formulation inhibited 88.21%. Figure [13] graphically illustrates this comparison, demonstrating the higher effectiveness of the test formulation in reducing paw swelling.

Table.6 % inhibition of paw edema for std and test

Time (Hrs)	% Inhibition edema (Std)	%Inhibition of edema (Test)
2	4.56	24.89
4	46.82	73.69
6	65.63	80.42
8	60.49	85.82
12	81.45	88.21

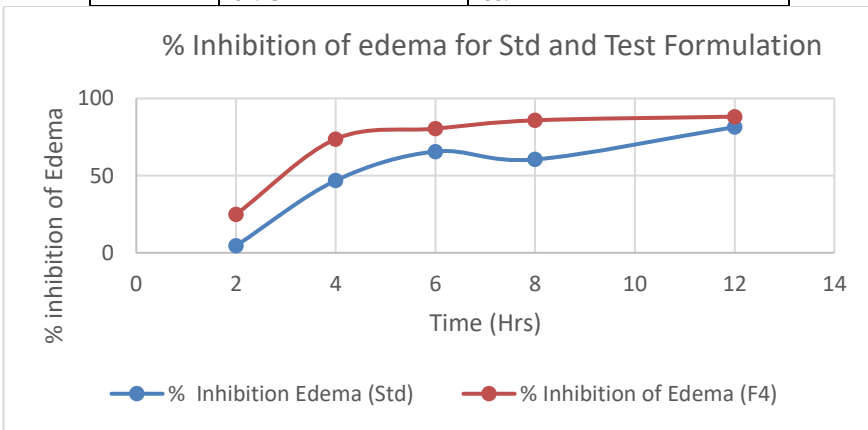


Fig 13. Graphical representation of % inhibition of edema for std. and test formulation

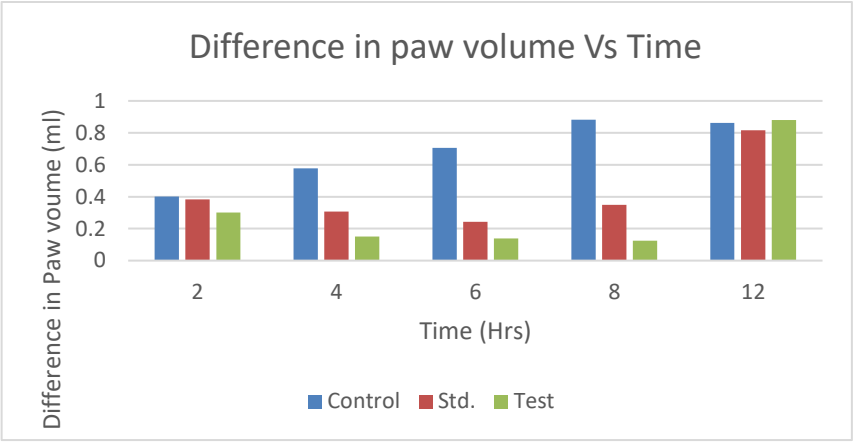


Fig. 14 Difference in paw volume Vs time

Stability Testing- The optimized formulation of the felbinac-loaded transdermal patch was subjected to stability testing for 6 months under ambient environmental conditions. The results demonstrated that there were no significant changes in the patch's physical appearance, drug release, or drug content during this period. This indicates that the formulation is stable and maintains its integrity over time.

4. Conclusion-

A novel transdermal drug delivery system for Felbinac was developed using transferosomes incorporated into an adhesive-type patch. The formulation was optimized to enhance drug permeation and release. In-vivo studies showed improved anti-inflammatory activity and excellent stability. This approach offers a promising solution for delivering poorly permeable drugs like Felbinac.

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