Formulation And Qbd-Driven Evaluation Of Apremilast Transferosomal Gel: A Systematic Approach

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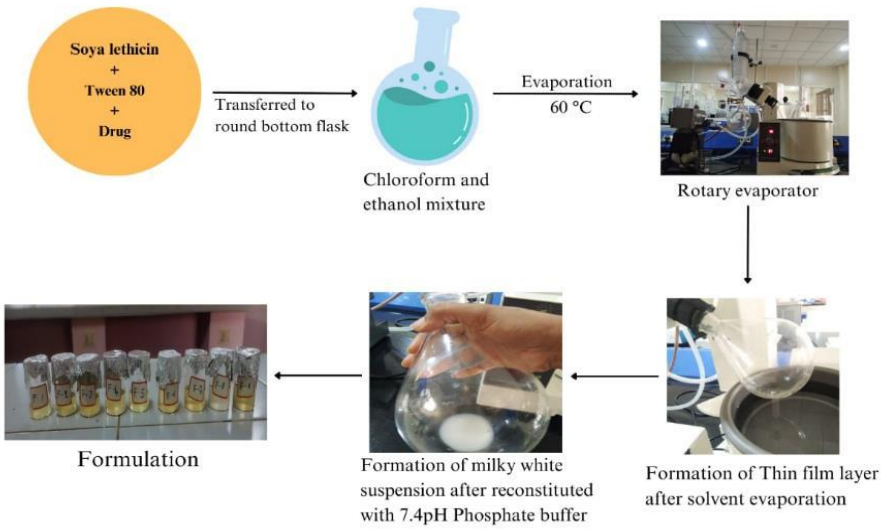
Abstract
Transfersomes are highly optimized ultra-deformable lipid aggregates, exceptionally flexible, and capable of penetration through mammalian skin intact. They are effective carrier systems for delivering both low and high-molecular-weight drugs transdermally. The present investigation was to formulate transferosomal gel which is an approach for the delivery of an Antipsoriatic drug, Apremilast. Apremilast, a new PDE4 inhibitor with additional TNF- α inhibitory properties, is presently undergoing clinical trials for potential use in treating psoriasis and various inflammatory disorders. Apremilast transfersomal gel was formulated and optimized by using a rotary evaporator. Initially, 9(F1, F2, F3, F4, F5, F6, F7, F8, F9) transferosomal formulations were prepared by using the approach of quality by design (QbD). A 2 level 2 factor, full factorial composite design was applied to formulate Apremilast transferosomes. Independent variables selected are Concentration (conc.) of Soya Lecithin and Tween 80. All were set at low level and high level. Responses were chosen as Particle size (PS), Polydispersity index (PDI) Zeta potential (ZP). QbD is a systematic method that can be utilized in formulation development. Out of 9 formulations, the optimized formulation F2 was selected because of its efficient entrapment efficiency, vesicle size, and zeta potential. The optimized formulation F2 was made into a transferosomal gel by using carbopol 934 as a gelling agent and in-vitro permeation studies were performed for about 12 hours by using a Franz diffusion cell apparatus, drug release at the end of the 6th hour was 79.5%.

GRAPHICAL ABSTRACT



Schematic representation of formulation process of Transferosomes

Keywords: Transferosomes ; Apremilast ; Psoriasis ; Transferosomal Gel ; Quality by design (QbD)

INTRODUCTION

Psoriasis affects approximately 2-3% of the global population , translating to over 125 million individuals . Around 75%of cases manifest before the age of 40. Approximately 70-80% of patients experience mild to moderate psoriasis , while 20-30% suffer moderate to severe forms.

Psoriasis an enduring autoimmune and non-communicable inflammatory disorder affecting both skin and joints, derives its name from the Greek roots "Psora," meaning itchiness, and "iasis," signifying a condition.[1] This ailment manifests through distinctively defined, scaly, red, coin-sized skin lesions, primarily found on areas like the elbows, knees, scalp, hands, and feet.[2] Symptoms encompass sensations of itching, irritation, stinging, and pain, occasionally extending to affect the entire body's skin surface. Certain medications, including beta-blockers, lithium, synthetic antimalarial, nonsteroidal anti-inflammatory drugs (NSAIDs), and tetracycline's, have been strongly linked to the onset or exacerbation of psoriasis. The inflammatory mechanisms are immune mediated associated with a series of linked cellular changes in the skin like hyper proliferation of keratinocytes, vascular hyperplasia, and infiltration of T lymphocytes, neutrophils, macrophages and other types of leukocytes.

The inflammatory mechanism includes that dendritic cells or Antigen Presenting Cells (APCs) detect stress signals emitted by keratinocytes upon contact with antigens. This triggers the differentiation of naive T cells into effector cells such as Th1, Th2, and Th17. Subsequently, each differentiated effector cell produces inflammatory cytokines such as interferon (IFN-α), tumor necrosis factor (TNF-α), and interleukin (IL-2).[3]

Due to the significant role of PDE4 in the regulation of inflammatory cytokines, researchers have explored various molecules as potential therapeutic agents capable of influencing this enzyme activity .Among these compounds apremilast has emerged as particularly promising and has been suggested for the treatment of psoriasis and PsA. Apremilast is a newly developed PDE4 inhibitor that also exhibits inhibitory effects on TNF-a. It is presently being clinically evaluated for its potential in treating psoriasis and various other inflammatory conditions. In recent times, there has been a notable increase in the licensing of newer small molecules for dermatological conditions among these, apremilast has garnered significant attention from dermatologists, due to its convenient administration via oral or topical routes, coupled with their acceptable efficacy and excellent safety profile. In contrast to biologic agents, small molecule drugs are relatively simple to synthesize and are more cost-effective to produce. Apremilast has been studied in a range of dermatological conditions, such as atopic dermatitis, lichen planus, alopecia areata, contact dermatitis, rosacea, sarcoidosis, and lupus erythematosus.[4]

Transdermal delivery offers several advantages over oral administration and hypodermic injections.[5] specifically, it is preferred when the liver's first-pass effect can prematurely metabolize drugs.[6] Unlike injections, which are painful, generate hazardous medical waste, and pose risks of disease transmission through needle reuse, transdermal delivery is non-invasive and can be self-administered. Additionally, transdermal systems provide sustained release over extended periods, up to a week, enhancing patient compliance. Moreover, these systems are generally cost-effective. To achieve systemic effects by delivering therapeutic agents through the human skin, it's essential to take into account the comprehensive morphological, biophysical, and physicochemical properties of the skin.

Transferosomes represent a specialized type of deformable vesicles utilized as drug delivery systems.[7] Engineered to facilitate the delivery of drugs with varying molecular weights, they emulate cellular vesicles or cells engaged in exocytosis, thus enabling precise and controlled drug delivery. Their potential lies in enhancing drug permeation through the skin and increasing bioavailability. Transferosomes exhibit the capability to encapsulate both hydrophilic and hydrophobic drugs, presenting a versatile platform for delivering a diverse array of therapeutic agents.[8] Transfersomes are composed of two main components: an amphipathic ingredient, such as phosphatidylcholine, which forms a lipid bilayer in water, creating a basic lipid vesicle; and a bilayer softening component, known as an edge activator (EA), which greatly enhances the permeability and flexibility of the lipid bilayer.[9] Due to their ultra-deformable and self-optimizing properties, transfersomes can easily deform and pass through narrow skin constrictions, even smaller than their own size.[10] In transferosomes, hydrophilic (water-preferring) drugs are encapsulated or adsorbed in the aqueous cavity at the centre of the vesicle, whereas hydrophobic (lipid-preferring) drugs are encapsulated between the phospholipid-lipid bilayer. Transfersomes present a versatile delivery approach, offering improved stability and compatibility with a wide range of active compounds. They exhibit metastability, rendering their vesicle membrane ultra-flexible, allowing easy penetration into the skin's stratum corneum.[11] Even sizes up to 200–300 nm can penetrate intact skin. However, the low viscosity of transfersomal suspensions limits their use in transdermal delivery due to handling challenges. Researchers have explored biocompatible gels with weak interactions with surfactants to modify the rheological properties of transferosomal suspensions. Incorporating transferosomal suspensions into a gel matrix can yield transferosomal gel formulations, potentially more suitable for transdermal applications.

2. MATERIALS AND METHODS

MATERIALS

Apremilast of analytical grade (purity,>98%) was a sample from Parkinson Pharma, Mohali, India. SoyaLecithin (LOBA CHEMI Laboratories-Mumbai), Tween 80 (LOBA CHEMI Laboratories-Mumbai), Ethanol (LOBA CHEMI laboratories, Mumbai) and chloroform (Merck Specialities Pvt. Ltd, Mumbai, India) were used. Distilled de-ionized water was used. All the materials used were of pharmacopoeial and analytical grades

METHODS

2.1Preformulation studies

Preformulation studies involve a sequence of investigations performed on a drug substance before the formulation stage. The primary objective is to analyse the physicochemical properties of the drug and its response to different environments. (T3)

2.1.1Physical appearance: The drug powder underwent evaluation for its sensory characteristics, including colour, taste, and odour.[12]

2.1.2Drug excipient compatibility study: Drug-excipient compatibility was assessed via Fourier Transform Infrared Spectroscopy (FT-IR). Spectral data obtained from Bruker FT-IR Germany were utilized to analyse the functional groups and the chemical structure of the drug and to detect potential interactions between the pure drug and excipients in the solid state. The spectra were recorded over the wave number of 4000 to $400\ cm^{-1}$.

2.1.3Determination of absorption maximum (λ_{max}): The λ_{max} of the drug was determined by dissolving 100mg of drug in 100ml of phosphate buffer ($p^H 7.4$) in 100ml volumetric flask. 1ml of this stock solution was pipetted into 10ml volumetric flask and make up the volume with phosphate buffer ($p^H 7.4$). The resulting solution was scanned in the UV spectrometer.[13]

2.1.4 p^H measurement: The pH was measured using a digital pH meter. In this procedure, 1 gram of Apremilast powder was precisely weighed and dissolved in 5 mL of ethanol. The solution was then diluted to 100 mL with distilled water using sonication. After filtration, the pH of the filtrate was determined using a digital pH meter.

2.1.5 Preparation of Apremilast calibration curve: 100mg of drug dissolved in ethanol and makeup with phosphate buffer of $p^H 7.4$ in 100ml volumetric flask. From the above stock solution 2ml, 4ml, 6ml,8ml and 10mlsolutions are taken and dissolved with 10ml of phosphate buffer and absorbance was measured.[14]

2.2 Design of experiments

A 2 level 2 factor (2^2) full factorial composite design was applied to formulate Apremilast transferosomes. Independent variables were selected as Concentration (conc.) of Soya Lecithin and Tween 80. All were set at low level and high level. Responses were chosen as Particle size (PS), Poly dispersity index (PDI) Zeta potential (ZP). The actual values and coded values of different variables were given in Table 2. According to factorial design, nine formulations (F1-F9) of transfersomes were manufactured.[15]

Table 1: Factors and responses

Formulations	Factor 1 A: Phospholipid mg	Factor 2 B: Tween 80 mg	Vesicle size (VS)	Poly dispersity index (PDI)	Zeta potential (ZP)
F1	8	0.3	675.8nm	0.325	-18.9mV
F2	25	0.3	212.0nm	0.930	-33.5 mV
F3	8	1	417.0nm	0.365	-28.7 mV
F4	25	1	410.3nm	0.412	-30.4 mV
F5	4.47918	0.65	537.9nm	0.819	-25.5 mV
F6	28.5208	0.65	357.1nm	0.437	-35.8 mV

F7	16.5	0.155023	3001.4nm	4.053	-10.6 mV
F8	16.5	1.14497	2467.7nm	3.685	-12.4 mV
F9	16.5	0.65	522.1nm	1.205	-20.3 mV

2.2 Formulation of Apremilast transferosomes

Transfersomes loaded with Apremilast were formulated by thin film hydration method by using rotary evaporator. Various amounts of soya lecithin, tween 80 and Apremilast (15mg) were dissolved in mixture of 5ml of ethanol and 5ml of chloroform. The solution was transferred to a round-bottom flask and dissolved by agitation. Subsequently, a thin film was formed by placing it in a rotating vacuum evaporator at 60°C. Remaining traces of solvent were removed under vacuum. Leave the formulation aside for 12 hours at room temperature. The lipid film deposited was hydrated with phosphate buffer of $p^H 7.4$ while rotating at 60 rpm for 2 hours at room temperature to form transfersomes.[16,17]

Table 2: Formulation table of Apremilast loaded transferosomes

S.NO	Formulation code	Drug (mg)	Soya lecithin (mg)	Tween 80 (mg)
1	F1	15mg	8	0.3
2	F2	15mg	25	0.3
3	F3	15mg	8	1
4	F4	15mg	25	1
5	F5	15mg	4.479	0.65
6	F6	15mg	28.520	0.65
7	F7	15mg	16.5	0.155
8	F8	15mg	16.5	1.144
9	F9	15mg	16.5	0.65

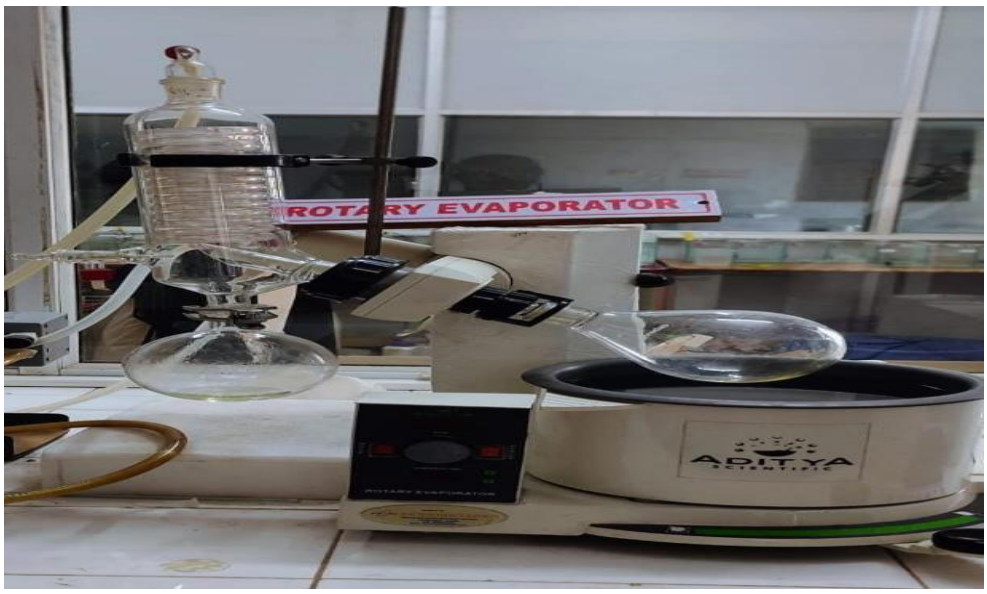


Figure 3: Rotary evaporator`

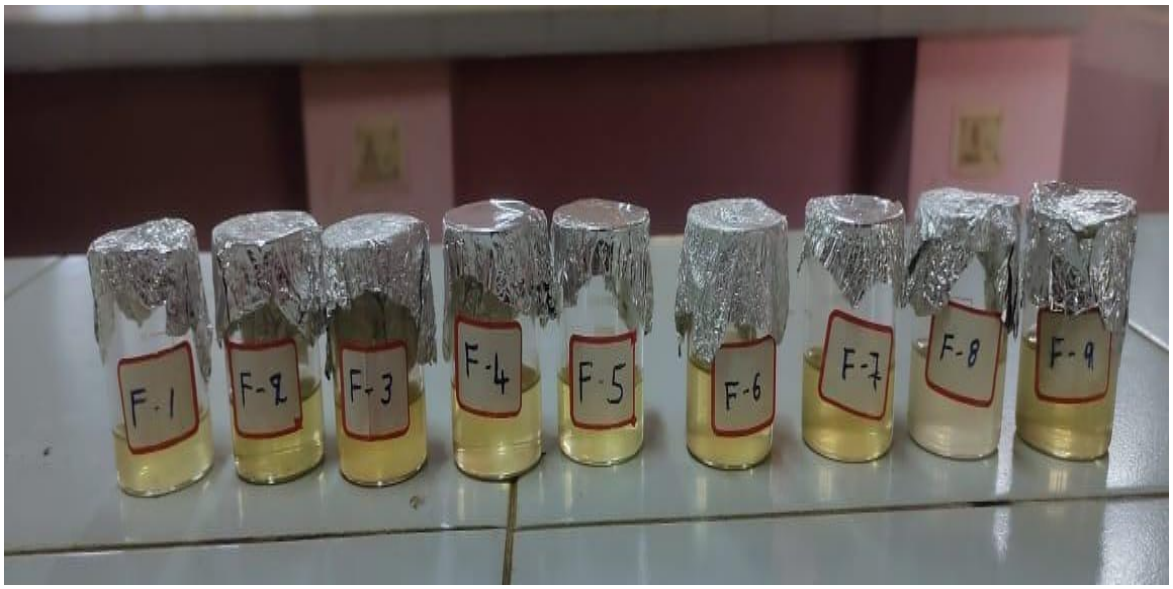


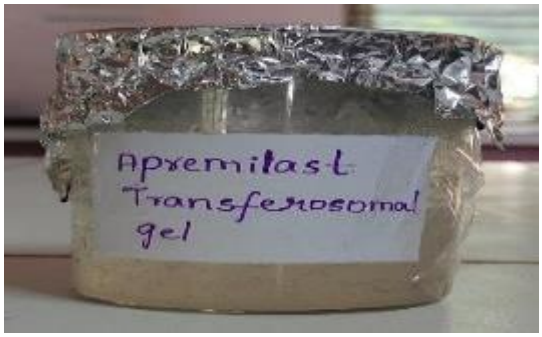
Figure 4: F1 to F9 formulations

2.3 Preparation of Carbopol gel base:

0.5 g of Carbopol 934 was weighed and dispersed in water with gentle stirring, few drops of triethanolamine was added to adjust p^H. Then left to swell for 24 hours to achieve a 0.5% carbopol gel.[18]

2.4 Preparation of Apremilast transferosomal gel:

The optimised transferosomes were incorporated into the 0.5% Carbopol gel base and constantly stirred with mechanical stirrer at 25 rpm for 10 mins.



2.5 Evaluation Apremilast loaded transferosomes

2.5.1 Vesicle size (VS), Poly Dispersity Index (PDI)

The size of the vesicles was measured by using particle size analyser (Horiba). First the cuvette was cleaned not to affect the analysis results. The samples were taken in cuvettes and measured the VS and PDI of transfersomes.[19]

2.5.2 Zeta potential (ZP)

The zetapotential was measured by using zeta sizer. Transferosomes were placed in washed and clean cuvette. Then ZP was measured from the electrophoretic mobility. The ZP vales were expressed in mv.[19]

2.5.3 Entrapment efficiency (EE):

The entrapment efficiency was assessed by quantifying the concentration of unentrapped drug in an aqueous medium. To achieve this, approximately 1.2 ml of the transferosomes dispersion containing the loaded apremilast was placed in Eppendorf tubes and subjected to centrifugation at 4000 rpm for 15 minutes.[20] This process resulted in the separation of transferosomes, along with the encapsulated drug, settling at the bottom of the tubes. Considering supernatant as stock solution, take 0.1ml of supernatant was diluted up to 10ml with phosphate buffer of P^H 7.4. The concentration of free drug was determined by measuring the UV absorbance of the resulting diluted solution at 340nm.[21]

2.6 Evaluation of apremilast loaded transferosomal gel

2.6.1 Appearance

The appearance was observed to assess the change by visual inspection colour, presence of foreign particles and homogenicity of the optimized transferosomes.[22]

2.6.2 P^H Determination

Using a digital p^H meter, the p^H of the prepared transferosomal gel was assessed. First the electrode was washed. A quantity of 50 grams of formulated gel was carefully weighed and transferred into a 10 ml beaker. The pH of the topical gel formulation was then measured using a digital pH meter. Determination of pH is important for the topical gel formulations to fall within the range of 3 to 9 in order to effectively treat skin infections.[23]

2.6.3 Viscosity

A Brookfield viscometer with spindle 52 was used to measure the viscosity of the F2 formulation. Let the formulation set for 30mins at room temperature in beaker. The spindle was lowered into the formulation at the centre, being careful not to contact the beaker bottom and revolved at a speed of 20rpm. The viscosity was recorded.[24]

2.6.4 Invitro drug release permeation studies

An in-vitro drug release study was conducted using modified Franz diffusion cells by using a cellulose membrane i.e. dialysis membrane. The membrane was soaked in phosphate buffer P^H 7.4 overnight. The membrane was taken off from the buffer. A dialysis membrane was positioned between the receptor and donor compartments which was pretreated. In the donor compartment, F2 formulation of transferosomal gel was placed, while the receptor compartment was filled with phosphate buffer at pH 7.4. The diffusion cells were maintained at a temperature of 37°C with stirring at 50 rpm throughout the experiment. At 15min, 30min, 45min, 1hr, 2hr, 3hr, 4hr, 5hr, 6hr ,7hr, 8hr,9hr,10hr,11hr,12hr time intervals. 3 ml aliquots were withdrawn from the receiver compartment through a side tube and subsequently analysed for drug content using a UV-visible spectrophotometer at 340nm.[25,26]

Figure5: Franz diffusion cell apparatus

3 RESULTS

3.1Preformulation Studies

3.1.1Determination of absorbance maxima (λ_{max}):

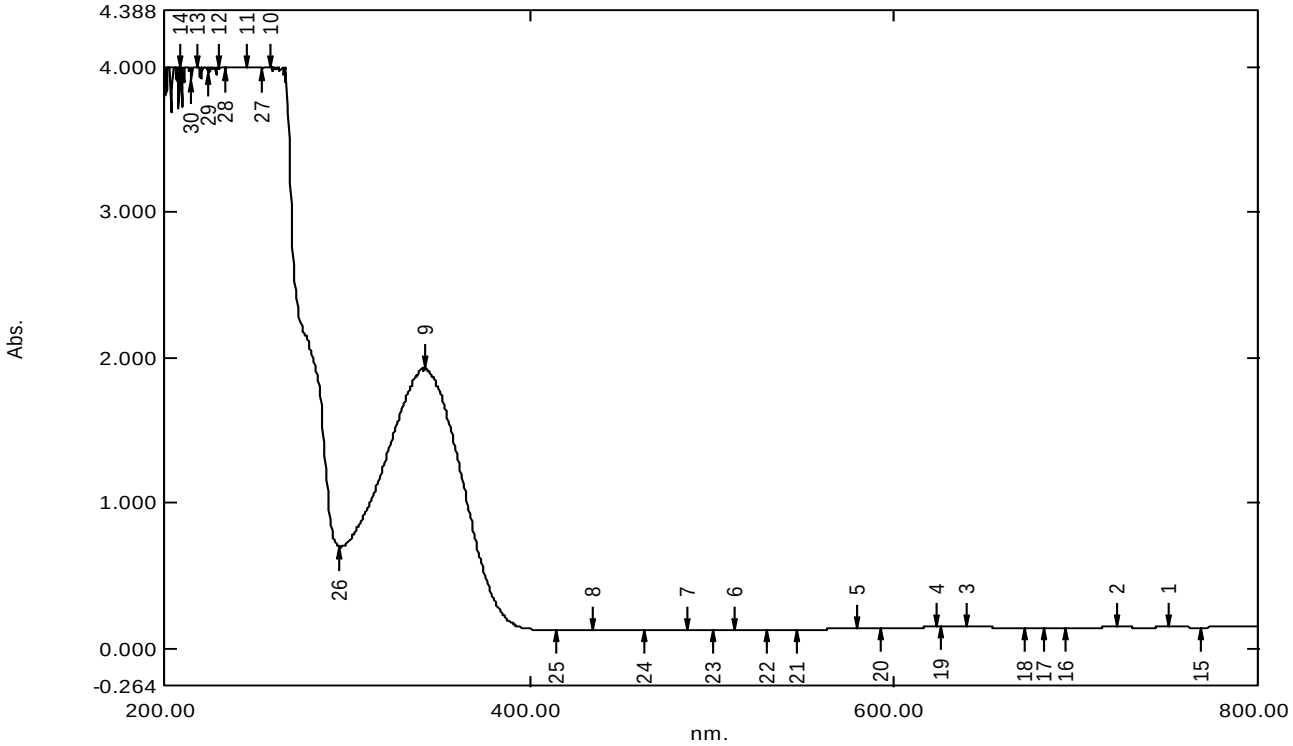


Figure 6: Absorbance maxima of Apremilast

3.1.2Drug excipient compatibility studies:

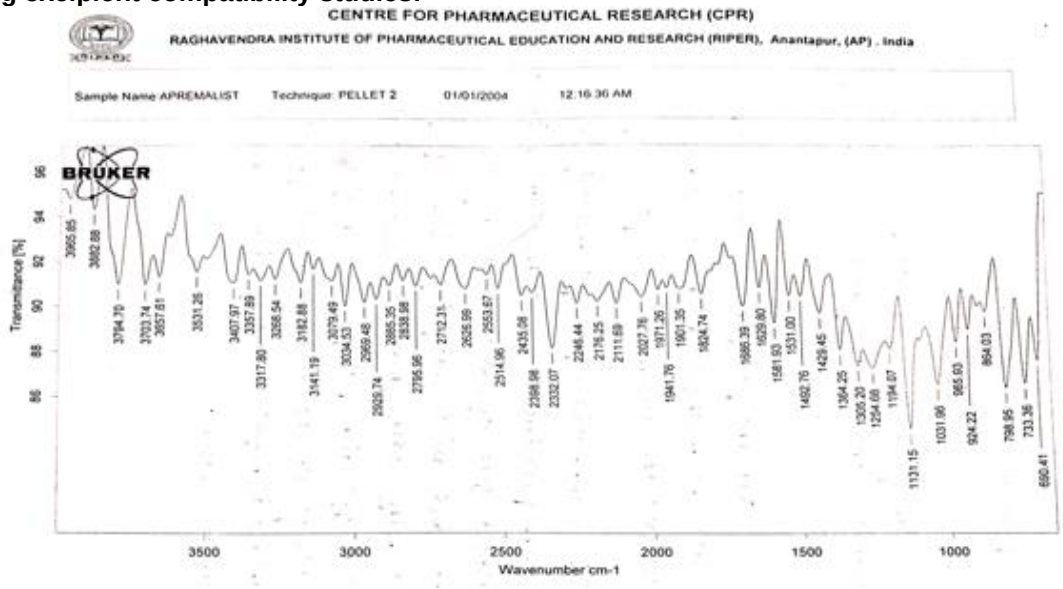


Figure 7: FT-IR spectrum of the apremilast

Table 3: FT- IR Ranges of the apremilast

Characteristic bands	Functional groups
3407	O-H (S)
1257	N-H(S)
1686	C=O(S)
1581	C=C(S)

a. FTIR of Soyalecithin

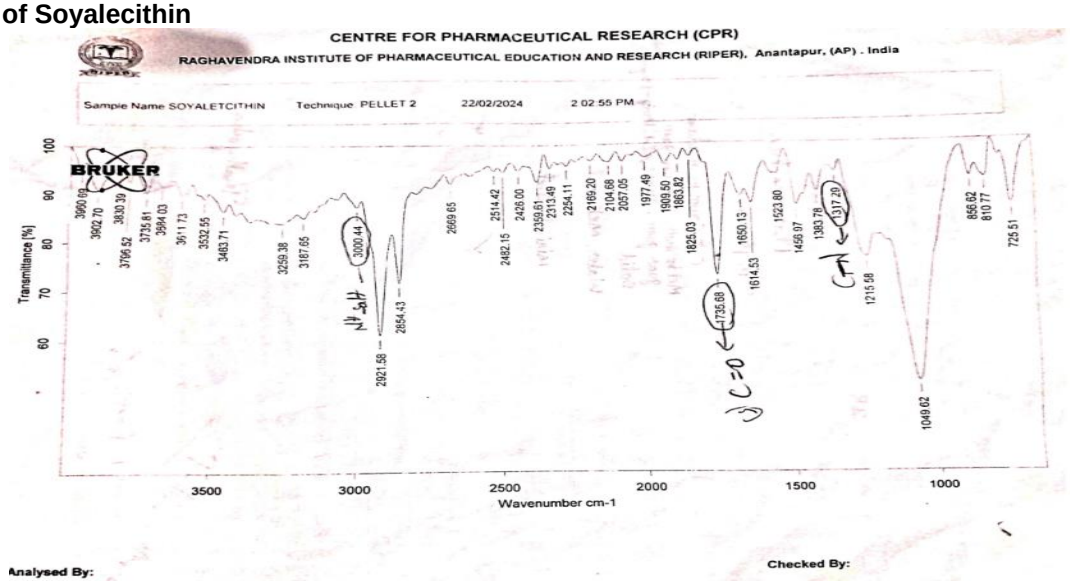


Figure 8: FT-IR spectrum of the soya lecithin

Table 4: FT- IR Ranges of the soya lecithin

Characteristic bands	Functional groups
1735	C=O(S)
1049	O-H(S)
1614	C=O(S)
1317	C=N(S)
2854	C-H(S)

b. FITR OF APREMILAST AND SOYA LECITHIN

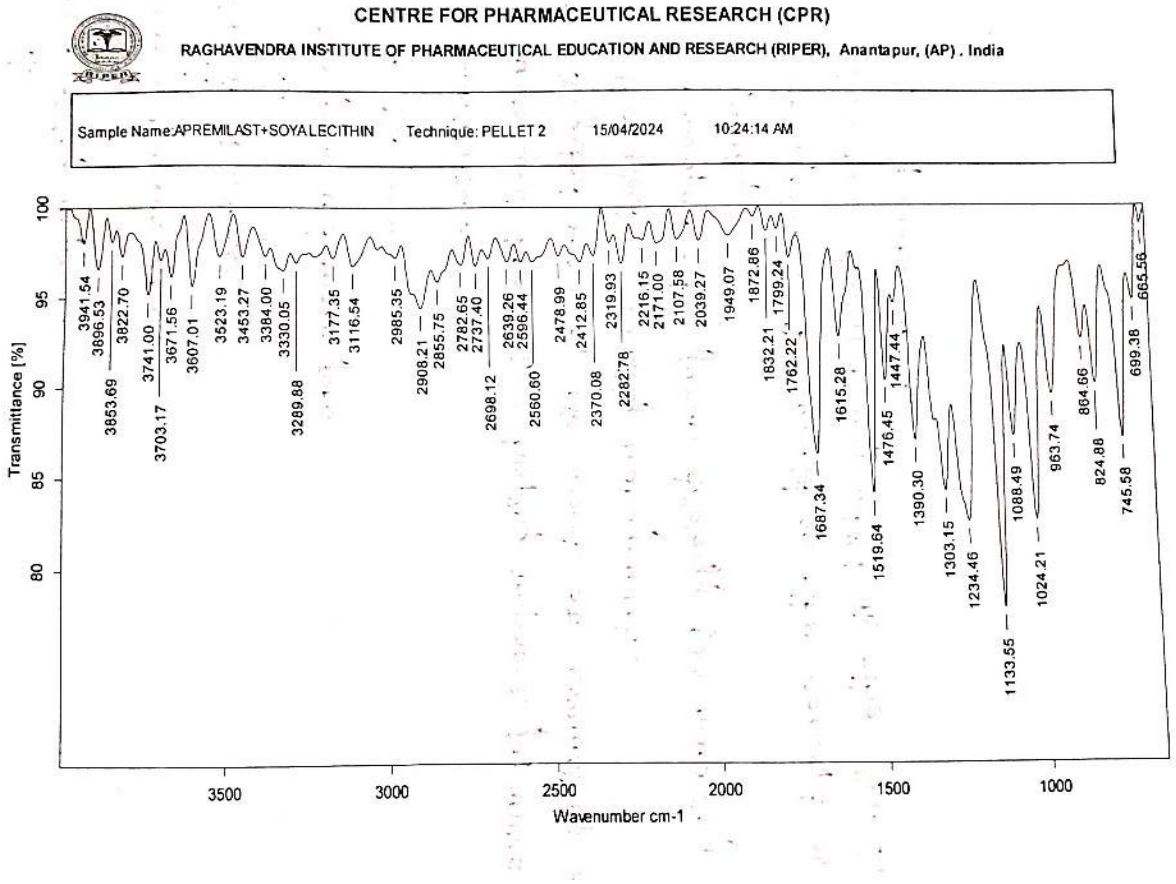


Figure 9: FT-IR spectrum of Apremilast and Soya Lecithin

Table 5: FT- IR Ranges of Apremilast and Soya Lecithin

Characteristic bands	Functional groups
3453	O-H(S)
1234	N-H(S)
1687	C=O(S)
1762	C=O(S)
2855	C-H (S)

3.1.3 Physical appearance

Table 6: Physical appearance of apremilast

colour	White
taste	Bitter
odour	Odourless

3.1.4 Preparation of Apremilast calibration curve:

Table 7: Concentrations of Apremilast

Concentration	**Absorbance**
200 µgm/ml	0.109
400 µgm/ml	0.175
600 µgm/ml	0283
800 µgm/ml	0.349
1000 µgm/ml	0.482

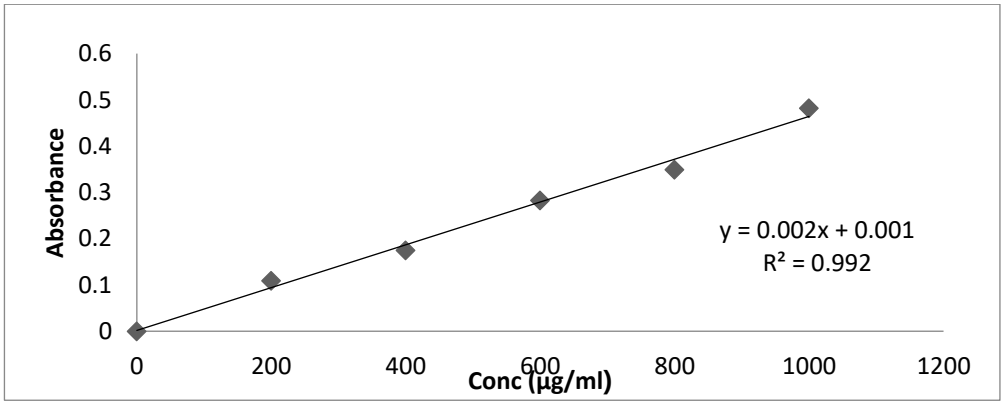


Figure 10: Graph of calibration curve

3.2EVALUATION OF APREMILAST TRANSFEROSOMES

3.2.1Determination of Vesicle size (VS), Poly dispersity index (PDI), Zeta potential (ZP)

Table 8: VS, PDI, ZP OF the formulations

Formulations	**Factor 1 A: Phospholipid mg**	**Factor 2 B: Tween 80 mg**	**Vesicle size (VS)**	**Poly dispersity index (PDI)**	**Zeta potential (ZP)**
F1	8	0.3	675.8nm	0.325	-18.9mV
F2	25	0.3	212.0nm	0.930	-33.5 mV
F3	8	1	417.0nm	0.365	-28.7 mV
F4	25	1	410.3nm	0.412	-30.4 mV
F5	4.47918	0.65	537.9nm	0.819	-25.5 mV
F6	28.5208	0.65	357.1nm	0.437	-35.8 mV

F7	16.5	0.155023	3001.4nm	4.053	-10.6 mV
F8	16.5	1.14497	2467.7nm	3.685	-12.4 mV
F9	16.5	0.65	522.1nm	1.205	-20.3 mV

3.2.2Entrapment efficiency (EE):

Table 9: EE of the formulations

Formulation	% EE
F1	67%
F2	85.3%
F3	77%
F4	77.8%
F5	73%
F6	82%
F7	60%
F8	58%
F9	72%

3.3EVALUATION OF APREMILAST TRANSFEROSOME GEL

3.3. 1 P^H , viscosity determination:

Table 10: p^H and viscosity of the F2 formulation of Apremilast gel

Formulation	**P^H**	**Viscosity**
F2	6.0	220cP

3.3.2 Appearance

Table 11: Appearance of transdermal gel formulation of F2

S.NO.	**Parameter**	**F2**
1	Colour	**Transparent**
2	Foreign particles	**(-)**
3	Homogenicity	****

(-) indicates absence of other particles; ** indicates homogenicity of the transdermal gel

3.3.3Invitro permeation studies:

Table 12: Invitro drug release permeation of F2 formulation

Time	Absorbance	Concentration(µg/ml)	Amount (mg)	% drug release
15min	0.680	339.5	6.79	15.3%
30min	0.699	349	6.98	25.7%
45min	0.697	348	6.96	35.2%
1hr	0.696	347	6.95	45.5%
2hrs	0.704	351	7.03	47.6%
3hrs	0.706	352	7.05	56.7%
4hrs	0.835	417	8.34	65.8%
5hrs	0.900	449.5	8.99	76.2%
6hrs	0.969	484	9.68	79.5%

Table 13 Invitro drug release of pure drug

Time	**% drug release of pure drug**	**% drug release of transferosomal gel**
15mins	10.5%	15.3%

30mins	15.7%	25.7%
45mins	25.7%	35.2%
1hr	35.8%	45.5%
2hrs	37.8%	47.6%
3hrs	39.7%	56.7%
4hrs	42.8%	65.8%
5hrs	45.7%	76.2%
6hrs	49.6%	79.5%

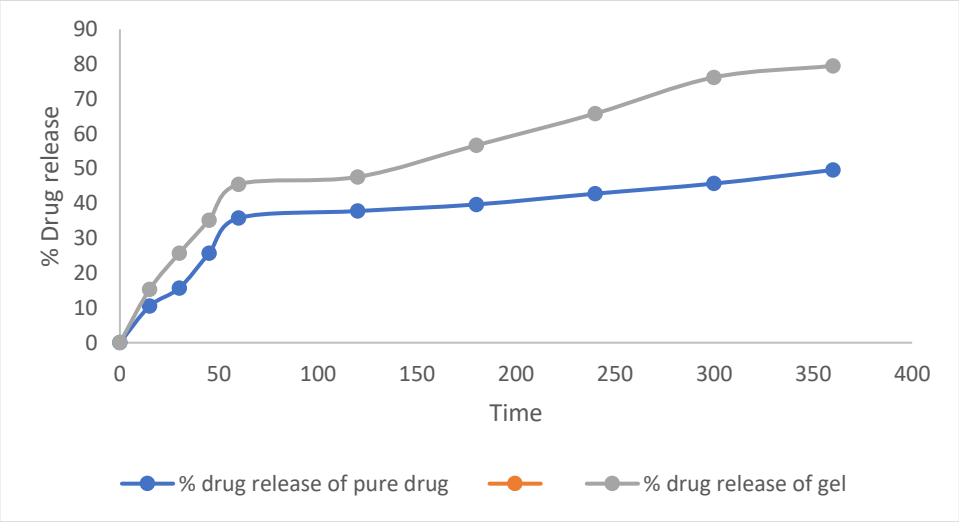


Figure 11: % drug release graph of pure drug and transferosomal gel

3.4 Response Y1 (Vesicle Size)

Table14: Statistical Design of experiments for Y1

Final equation in terms of coded factor for vesicle size

Vesicle size = +245.50+148.48A-177.08B-165.05AB+193.17A^2+90.59B^2

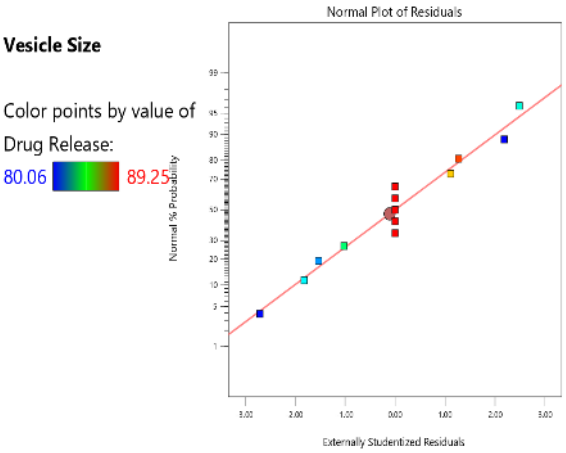


Figure 12: Normal plots of resudials in vesicle size

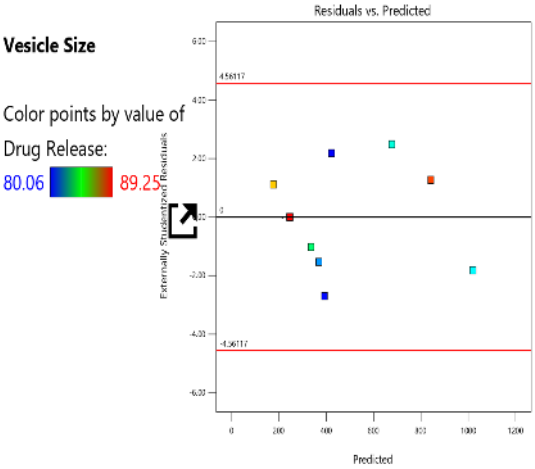


Figure 13: plots of residuals Vs predicted in vesicle size

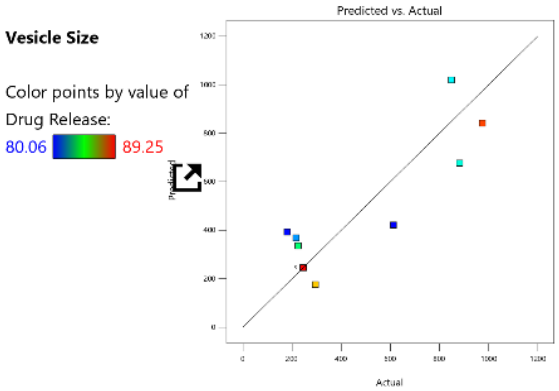


Figure 14: Plots of predicted Vs actual in vesicle size

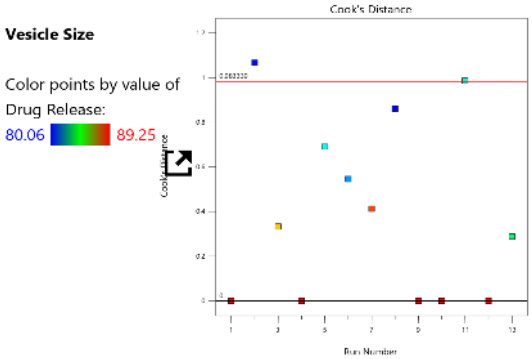


Figure 15: Plots of Cooks distance in vesicle size

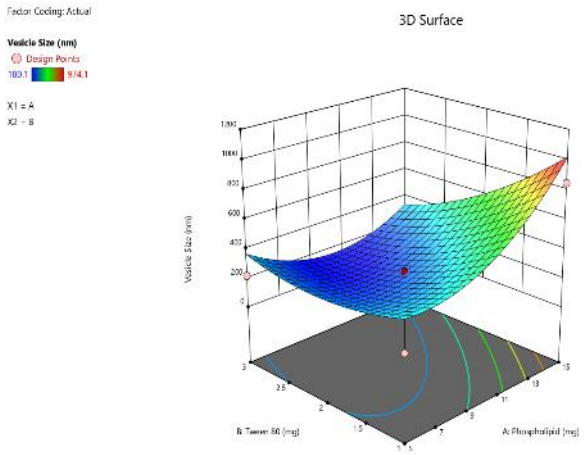


Figure 16: 3D structure in vesicle size

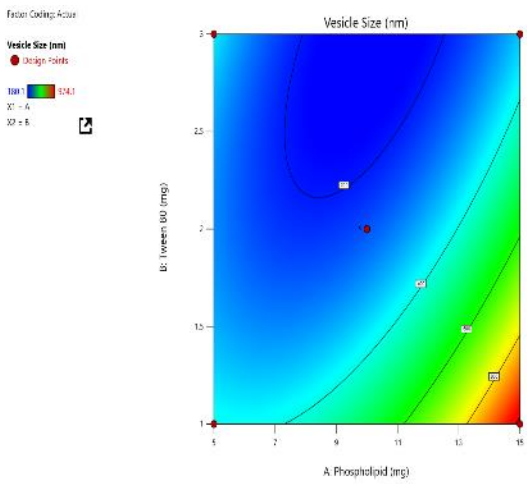


Figure 17: Structure of Phospholipid

Response Y2 (Poly dispersity index)

Final equation in terms of coded factor for Poly dispersity index

Poly dispersity index =+0.3640+0.0468A-0.0050B-0.0340AB-0.0188A^2 +0.0703B^2

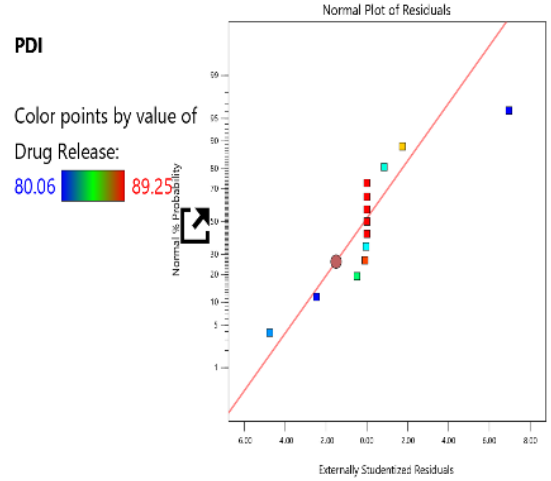


Figure 18: Normal plots of residuals in PDI

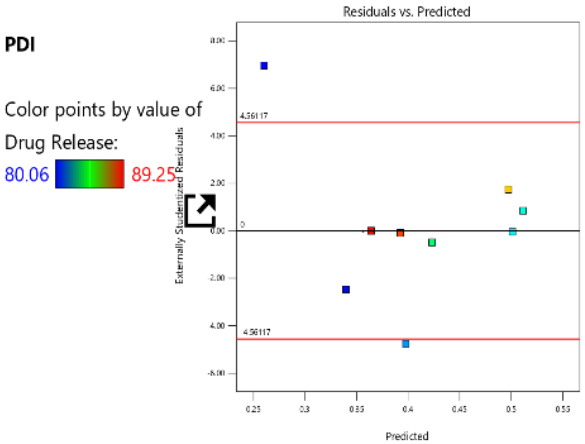


Figure 19: plots of residuals VS Predicted Value

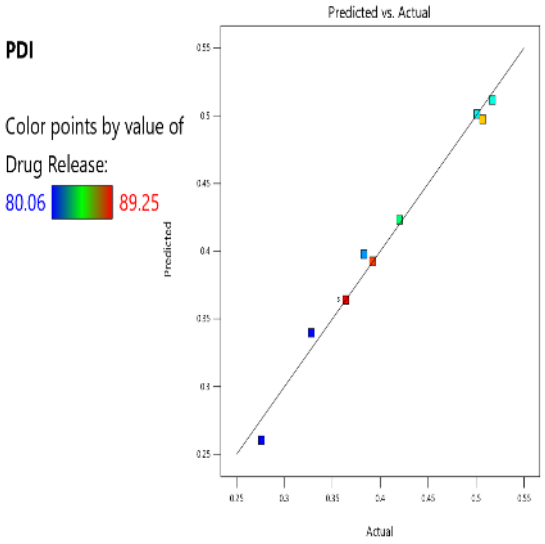


Figure 20: Plots of predicted Vs actual in PDI

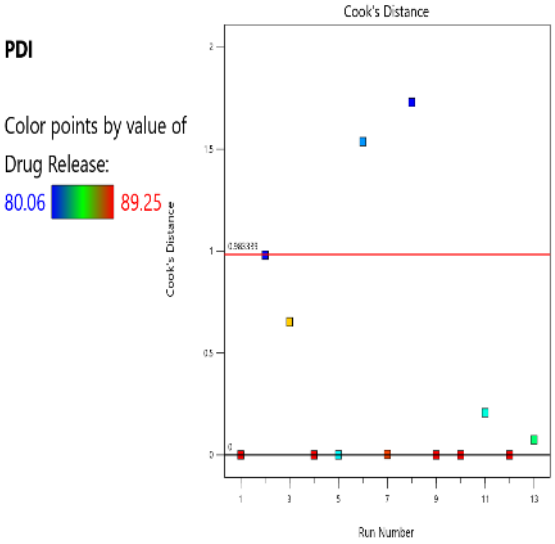


Figure 21: Plots of Cooks distance in PDI

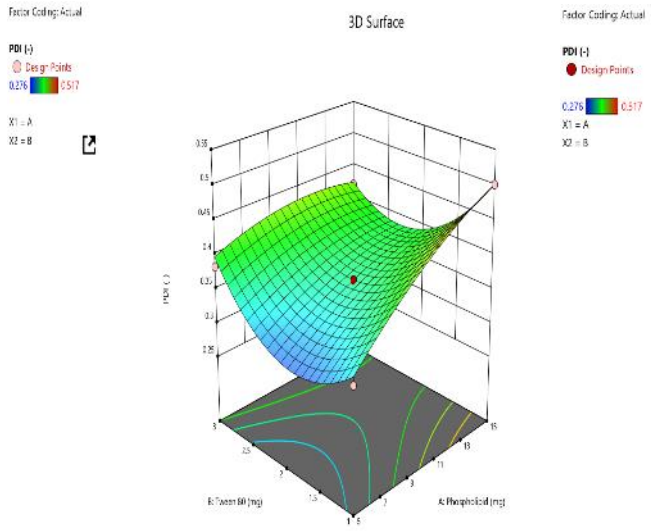


Figure 22: 3D structure in PDI

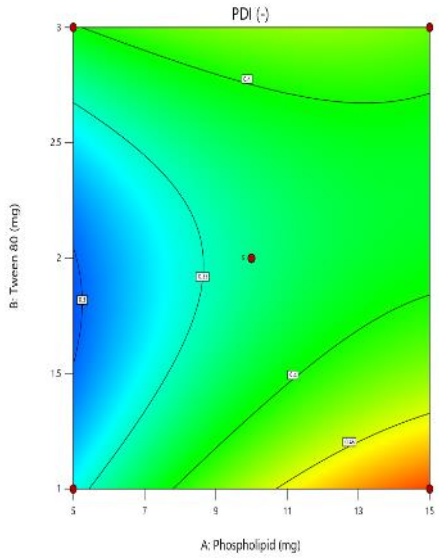
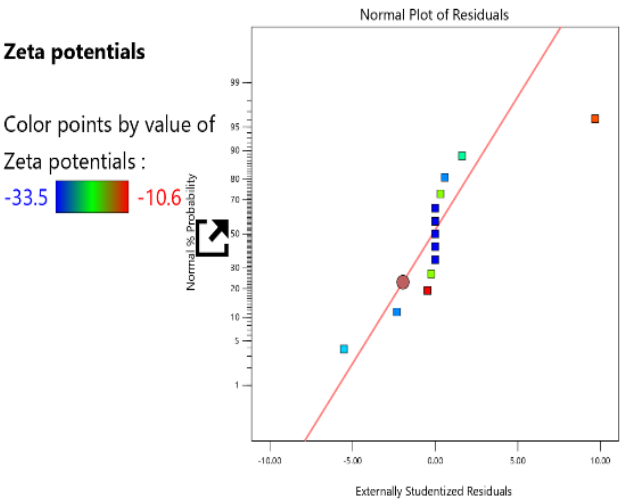
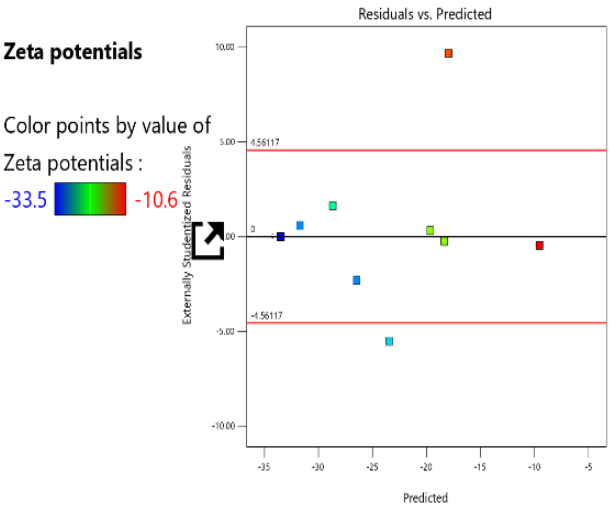
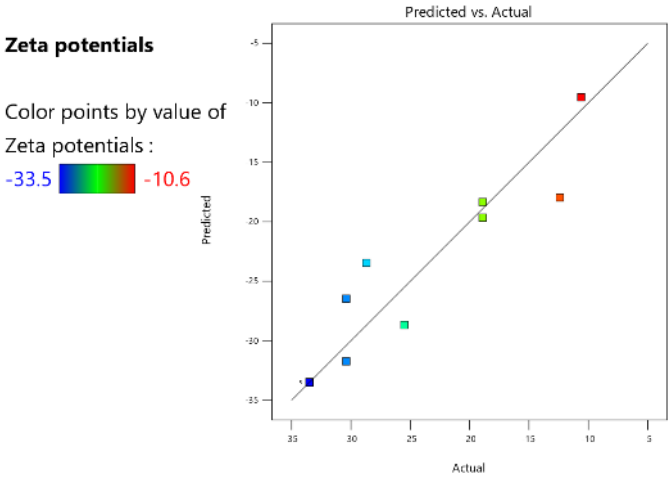


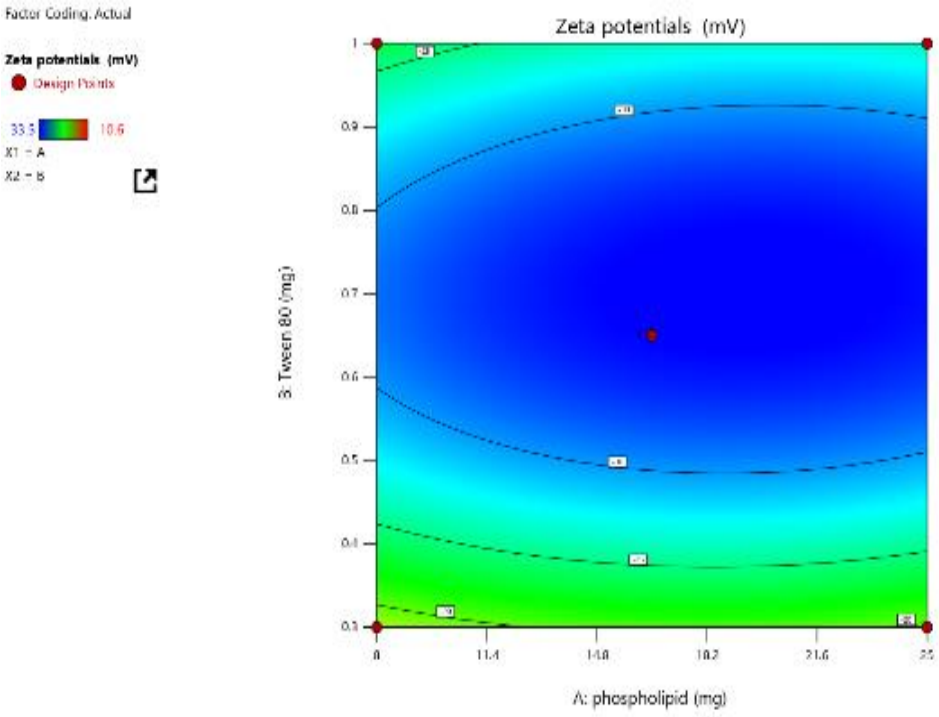
Figure 23: Structure of Tween 80

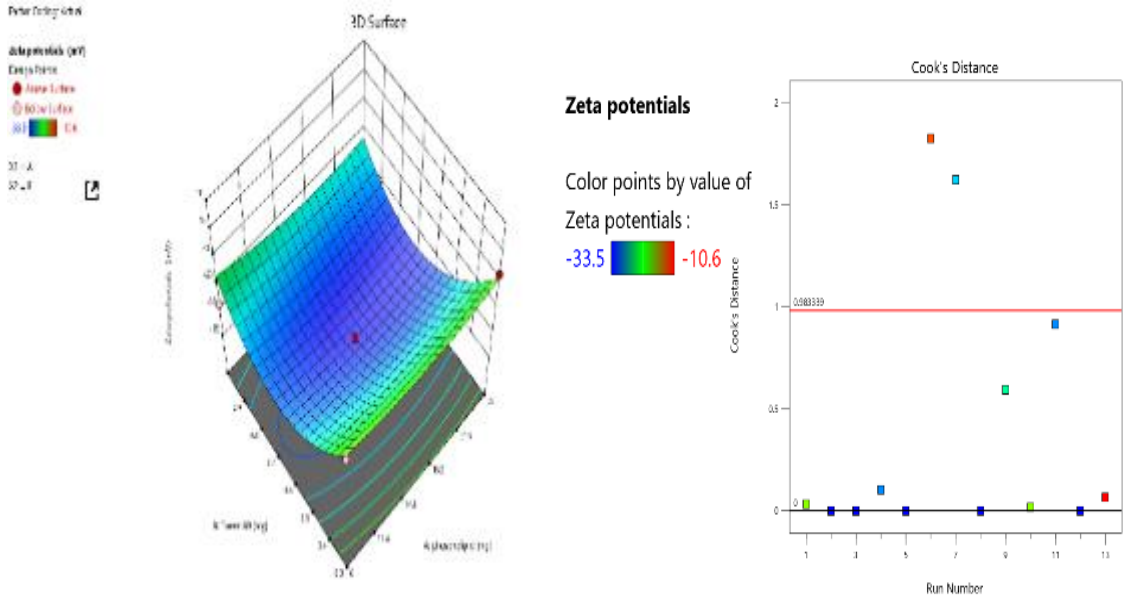
Response Y3 (Zeta potential)






Zeta potentials
Color points by value of
Zeta potentials :
-33.5
-10.6
Predicted vs. Actual
Predicted
Actual


Factor Coding: Actual
Zeta potentials (mV)
Design Points
33.3
10.6
X1 = A
X2 = B
Zeta potentials (mV)
B: Tween 80 (mg)
A: phospholipid (mg)



4 DISCUSSIONS

4.1Physical Appearance

The physical appearance of the Apremilast include colour, taste, odour which were white, bitter, and odourless as shown in the (**Table 6)**.

4.2Drug excipient compatibility studies

FT-IR is used to study the drug excipient compatibility studies. **(Figure 7)** shows that FT-IR spectrum of Apremilast showed no major shifts of the peaks used in the formulation. The major functional group frequencies of Apremilast showed peaks at 3407nm, 1254nm, 1686nm, 1581nm corresponding to O-H (S) group, N-H(S) group, C=O(S) group, C=C(S) group respectively which were reported without any deviations with the mixture. The functional groups and the characteristic bands are tabulated in **(table 3). (Figure8)** shows that FT-IR spectrum of Soya Lecithin showed no major shifts of the peaks used in the formulation. The major functional group frequencies of methocarbamol showed peaks at1735nm, 1049nm, 1614nm, 1317nm, 2854nm corresponding to C=O (S) group, O-H(S) group, C=O(S) group, C=N(S) group, C-N(S) group respectively which were reported without any deviations with the mixture. The functional groups and the characteristic bands are tabulated in (**table 4)**. **(Figure 9)** shows that FT-IR spectrum of Apremilast and Soya Lecithin showed no major shifts of the peaks used in the formulation. The major functional group frequencies of methocarbamol showed peaks at3453nm, 1234nm, 1687nm, 1762nm, 2855nm corresponding to O-H(S) group, N-H(S) group, C=O(S) group, C=O(S) group, C-H(S) group respectively which were reported without any deviations with the mixture. The functional groups and the characteristic bands are tabulated in (**table 5).**

4.3Analytical method development:

The analytical method development was performed for the pure drug of the apremilast by UV spectroscopy and the standard graph was plotted as shown in the **Figure 10.** The concentration and the absorbance were tabulated in **Table 7.**

4.4Absorbance maxima

The absorbance maxima were performed for the pure drug of apremilast by UV spectroscopy and the graph was shown in the **Figure 6.** The maximum absorbance was found to be 340nm.

4.5Vesicle size (VS)

The vesicle size of the transferosome formulations (F1-F9) was found to be in the range of 200nm to 3000nm **(Table 8).**

4.6Polydispersity index (PDI)

The PDI of the transferosome formulation (F1-F9) was found to be in the range of 0.3 to 4.0 **(Table 8).** The optimum level of soya lecithin and tween 80 is considered as the main factor responsible for the reduction in particle size and decreased polydispersity index because its inclusion in the formulation lead to reduction in viscosity and surface tension that helped in the formation of nano sized homogenously distributed

nanoparticles. It can be observed that the slight increase or decrease in the concentrations of soya lecithin and tween 80 lead to the changes in poly dispersity index.

4.7Zeta potential (ZP)
The ZP of the transferosomes formulation (F1-F9) was found to be in the range of -10 to -35mV **(Table 8).**

4.8Entrapment efficiency (EE)
The EE was performed to transferosomes formulation (F1-F9) was found to be at the range of 60 to 85% **(Table 9)**.
The free drug concentration was calculated using the straight-line equation
i.e y=0.002x + 0.001
The free drug concentration =176mcg/ml
EE% = $W_{(\text{Total drug})} - W_{(\text{Free drug})} / W_{\text{Total drug}} \times 100$

4.9P^H
The P^H of the formulated gels i.e., F2 was determined as 6.2**(Table 10).** Triethanolamine balanced the skin P^H. As there was no sign of any phase separation the formulations can be utilized for application on human skin.

4.10Viscosity
The formulation F2 showed good viscosity **(Table 10).** The concentration and the nature of gelling agent leads to the changes in viscosity.

4.11Appearance
The formulation F2 were transparent, free from foreign particles and homogenous in nature **(Table 11).**

4.12 Invitro permeation studies
The apremilast transferosomal formulation F2 exhibit better vesicle size, PDI and zeta potential. And the F2 formulation have highest %EE i.e 85.3%. So, the F2 formulation is further developed into transferosomal gel. The F2 formulation exhibits the invitro permeation studies by using Franz diffusion cell apparatus. By the end of 12th hour, the % drug penetration was 85.5%**(Table12).** The invitro permeation studies are conducted to the pure drug. By the end of the 12th hour, the % drug release was 49.6% **(Table 13)**. The graph is plotted between the % drug penetration per unit area the cellulose membrane and time for both pure drug and the transferosomal gel containing apremilast **(Figure11).**

CONCLUSION
The transferosomes of apremilast was formulated by thin film hydration method which is further formulated as transferosomal gel. In preformulation the FTIR studies were conducted for API and excipients to determine the functional groups and chemical structure, and interaction between the drug and excipients.
Total 9 formulations were prepared by using various amounts of soya lecithin and tween 80 and evaluated for vesicle size and entrapment efficacy. The formulation F2 contain the smallest vesicle size and 85% of entrapment efficacy. This is considered as optimized formulation for further evaluation.
The optimised formulation was converted in to transferosomal gel by using Carbopol 934 as gelling agent. The formulated gel was evaluated for viscosity and % drug release. The ph was found to be 6.0 which is nearly equal to the skin. The viscosity was found to be 220cP.
The %drug release determined by Franz diffusion cell. By placing the gel in diffusion apparatus and withdrawing the samples at 15min, 30min, 45min, 1hr, 2hr, 3hr, 4hr, 5hr, 6hr,7hr,8hr,9hr,10hr,11hr,12hr and the % drug release was 15.3%, 25.7%, 35.2%, 45.5%,
47.6%, 56.7%, 65.8%, 76.2%79.5%, respectively. The % drug release values for the pure drug was 10.5%, 15.7%, 25.7%, 35.8%, 37.8%, 39.7%, 42.8%, 45.7%, 49.6% for 15min, 30min, 45min, 1hr, 2hrs, 3hrs, 4hrs, 5hrs, 6hrs respectively. From the result the transdermal gel loaded with apremilast shows more %drug release than the pure drug.

5. Acknowledgement :
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