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Formulation, Development and Evaluation of Topical Microemulsion Based Spray of Roflumilast

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ABSTRACT:- The objective of present research work was to formulate microemulsion spray of Roflumilast for the treatment of psoriasis. Roflumilast microemulsion spray was prepared and optimized, by using simplex lattice design. Spectrometric analysis of Roflumilast was done by using UV- Visible spectrophotometer and Drug-Excipients compatibility study was conducted by Fourier transform infrared spectroscopy. Oil, surfactant, and co-surfactant were selected based on the results of a solubility study for the formulation of microemulsion, while the ratio of surfactant to co-surfactant (Smix) was determined through pseudo-ternary phase diagram study. Roflumilast microemulsions spray were prepared by phase titration method. Simplex Lattice Design was applied using Design Expert 22.0.3.0 software. Concentration of Oil (X1) and Concentration of Smix (X2) and Concentration of Water (X3) were chosen as independent variables, while % Transmittance (Y1), Globule Size (Y2) and % Drug Diffusion (Y3) were selected as dependent variables. All seven microemulsion spray were evaluated further for different parameters such as pH, Viscosity test, centrifugation study, Polydispersity Index, spray pattern, Drug content and %drug diffusion. Check point batch was prepared and evaluated for the validation of model. Optimized microemulsion was evaluated for Globule size, Polydispersity index (PDI) and zeta potential. Optimized microemulsion was transferred into a spray Bottle and evaluated for different parameters such as color, homogeneity, consistency, pH, viscosity, % drug release and % drug content. Microemulsion spray was subjected to stability study under accelerated condition for one month.

Key words: Psoriasis, Roflumilast, Microemulsion, Simplex lattice design, Microemulsion spray.

I. INTRODUCTION TO DISEASE

Introduction[1][2] **:-**Psoriasis is a severe inflammatory skin disorder which affects 2-5% of world's population. It is an autoimmune skin disease which occurs in humans as result from interaction between genetics, dysfunctional immune system, environmental factors and skin barrier disruption. It can affect the males and females of any age. Psoriasis results in overproduction of skin cells and mainly characterized by thick, rough and scaly skin, appearance of red spots, lesions due to hyperkeratosis, dilated dermal blood capillaries, parakeratosis. It is present on elbows, knees, scalps, hands, legs, face etc. It affects patients physically and emotionally.

Advantages of Microemulsion Spray [11]

- It improves penetration of drugs across skin.
- Good loading capacity.
- It is easy to manufacture.
- Low production cost. Administration of both lipophilic and hydrophilic drugs.
- No extensive sonication is required.
- It is less oily and easy to remove.
- As it is applied topically it avoids GIT irritation and first pass metabolism.
- Noninvasive and improve patient compliance.

Limitation of Microemulsion Spray [11]

- Absorption through the skin is challenging for drugs with larger Globule Size
- Certain medicines exhibit low permeability when applied to the skin.
- It is suitable only for low dose medications.
- Allergic reactions may occur.
- Enzymes in the epidermis can denature drugs.

Preparation of microemulsion

Two techniques are used for preparation of microemulsion.
(1) Low energy emulsification technique
(2) High energy emulsification technique

(1) Low energy emulsification technique- It involves phase titration method and phase inversion method.

Phase titration method- It is mainly used for preparation of microemulsion. It is also termed as

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Volume 10, Issue 5 Sept - Oct 2025, pp: 389-401 www.ijprajournal.com ISSN: 2456-4494

spontaneous emulsification method. It is represented by pseudo ternary phase diagram. Drug that shows maximum solubility in oil, surfactants and co-surfactants are mainly selected for the preparation of microemulsion. Drug is dissolved in oil. Mixture of drug, oil, surfactant and co-surfactant is stirred at room temperature under magnetic stirrer and water is added dropwise. Cloudy or clear form is endpoint of this titration. The amount of water needs for it is recorded. The concentration of oil, surfactant and co-surfactant mixture and water is plotted on pseudo ternary phase diagram. Lastly microemulsion region area is observed from the diagram.

Phase inversion method- Addition of excess amount of dispersed phase or effect of temperature result in phase inversion of microemulsion. Phase inversion causes the alteration in physical property like Globule size, which eventually affects the drug release. Curvature of surfactant changes as changes in temperature. So oil in water microemulsion converts into water in oil microemulsion by low to high temperature. While undergoing the cooling process, the system reaches a stage where there is zero spontaneous curvature and minimal surface tension, facilitating the creation of finely dispersed oil droplets. This method is termed as Phase Inversion Temperature (PIT) method. Other properties like pH and salt concentration are also considered. Increasing the water amount changes the spontaneous curvature of the surfactant and results in a w/o microemulsion to an o/w microemulsion.

(2) High energy emulsification technique- External energy is applied for the formulation of microemulsion. Ultra sonicator and hard-hitting homogenizer are used for application of shear force.

Preparation of Spray:-

- Micro emulsion is filled in the container and it is capped with a sterile lid which contains actuator and valve like aerosol.
- Then the micro emulsion is sprayed through actuator in a uniform pattern.
- Evaluation Parameters must be carried out for Microemulsion and spray.

PREFORMULATION STUDY OF DRUG

Characterization of organoleptic characteristics of drug

Roflumilast was evaluated for color, odor, and nature.

Determination of melting point of drug [46]

Melting point of drug was determined using Veego melting point apparatus. Small quantity was inserted in a capillary tube that was sealed at one end and positioned within the melting point apparatus. The temperature at which the drug melted was noted.

FT-IR Study

IR spectral analysis of Roflumilast was done by Fourier transform infrared spectrophotometer (Shimadzu 8400S, Japan). Sample was scanned between 4000-400 cm-1. FT-IR spectra of Roflumilast were obtained.

SPECTROMETRIC ANALYSIS OF ROFLUMILAST [46]

In the present research work, Roflumilast was estimated by UV/Visible spectrophotometry. The drug release study was carried out using phosphate buffer pH 6.8.

Preparation of standard stock solution in Methanol

Accurately weighed 50 mg Roflumilast was taken and transferred into volumetric flask containing 50 ml methanol to prepare primary stock solution (1000 µg/ml). From primary stock solution 1 ml was taken and transferred into 10 ml volumetric flask and diluted up to 10 ml with methanol to prepare 100 µg/ml secondary stock solution.

Calibration curve of Roflumilast in Methanol.

From above solution prepare 10 µg/ml and scanned for absorbance between 200-400nm to determine UV absorbance Maxima. 0.5,1.0,1.5,2.0,2.5 and 3.0 ml of secondary stock solutions were taken and diluted up to 10 ml with methanol to get 5 µg/ml, 10 µg/ml, 15 µg/ml, 20 µg/ml, 25 µg/ml and 30 µg/ml respectively.

The absorbance of each solution was measured at 250 nm against methanol as a blank.

Calibration curve of Roflumilast in Methanol

0.5,1.0,1.5,2.0, 2.5 and 3.0 ml of secondary stock solutions were taken and diluted up to 10 ml with methanol to get 5 µg/ml, 10 µg/ml, 15 µg/ml, 20 µg/ml, 25 µg/ml and 30 µg/ml respectively.

The absorbance of each solution was measured at 250 nm against methanol as a blank.

International Journal of Pharmaceutical Research and Applications
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Preparation of standard stock solution in phosphate buffer pH 6.8

Preparation of Phosphate buffer

Weigh accurately 28.80gm of Disodium hydrogen orthophosphate and Potassium dihydrogen orthophosphate Dissolve the weighed amount of ingredients to a 1000ml volumetric flask.

Take 200ml of 0.1N NaOH Solution and add 600ml from 1000ml volumetric flask, Make up the volume up to 1000ml.

Preparation of stock solution

Accurately weighed 50 mg Roflumilast was taken and transferred into volumetric flask containing 50 ml methanol and 45ml phosphate buffer to prepare primary stock solution (1000 µg/ml.) From primary stock solution 1 ml was taken and transferred into 10 ml volumetric flask and diluted up to 10 ml with phosphate buffer pH 6.8 to prepare 100 µg/ml secondary stock solution.

Calibration curve of Roflumilast in phosphate buffer pH 6.8

0.5,1.0,1.5,2.0, 2.5 and 3.0 ml of secondary stock solutions were taken and diluted up to 10 ml with phosphate buffer pH 6.8 to get 5 µg/ml, 10 µg/ml, 15 µg/ml, 20 µg/ml ,25 µg/ml and 30 µg/ml respectively.

The absorbance of each solution was measured at 250 nm against phosphate buffer pH 6.8 as a blank.

SOLUBILITY STUDY[36]

Solubility study was conducted to determine appropriate Oil, Surfactant and Co-Surfactant for preparation of micro emulsion. Solubility of Roflumilast was determined in different Oils, Surfactants and Co- surfactants. Excess amount of Roflumilast was introduced into vials containing either oil, surfactant or co-surfactant. Vials were sealed with caps and subjected to vortexing for 10 minutes in order to facilitate proper mixing of Roflumilast with the excipients. Vials were shaken using a mechanical rotary shaker for 72 hrs with 150 rpm at 37º C. Subsequently, the vials were centrifuged at 3000 rpm for 15 min to obtain a supernatant liquid. Supernatant was passed through a 0.45µm membrane filter. Then filtrate was appropriately diluted with methanol. The concentration of Roflumilast in filtrate was obtained by UV Spectrophotometer at 250 nm.

DRUG EXCIPIENTS COMPATIBILITY STUDY

The infrared spectra of Roflumilast with mixture of excipients was recorded on Fourier transform infrared spectrophotometer (Shimadzu 8400S, Japan). Sample was scanned between 4000-400cm-1.

PSEUDOTERNARY PHASE STUDY [37]

The presence of microemulsion region was established through the utilization of a pseudo ternary phase diagram Pseudo ternary phase diagrams were created in order to determine concentration range of excipients like oil, surfactant and co-surfactant needed for the formulation of micro emulsion. Pseudo Ternary Phase Diagrams were constructed by using the phase titration method. The weight ratios of surfactant to co-surfactant (Smix) were varied as 1:1,2:1,3:1,1:2 and 1:3. Each Smix was blended with oil at varying weight ratios (Oil: Smix) including 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1. Water was added drop by drop to the mixture under magnetic stirrer until the mixture became turbid. The quantity of water was recorded. The concentrations of components were plotted on the pseudo ternary phase diagram by using Chemix software 12.2.

METHOD OF PREPARATION OF MICROEMULSION SPRAY [45]

Phase Titration method is used for the preparation of Microemulsion spray.

The formulation was prepared by dissolving the required amount of Roflumilast in Oil and Smix mixture by constant stirring, Methyl Paraben is used as a preservative. Then water was added into the mixture drop by drop under constant stirring until a clear solution is obtained. Then the optimized formulation will be transferred in to a spray bottle to make the application of microemulsion easy.

OPTIMIZATION OF MICROEMULSION BY USING SIMPLEX LATTICE [48] [49]

The number of runs and Formulation should be low as possible. The Simplex Lattice Design is applied for the determination of the relationship between the independent and dependent variables (response variable).

The selected response variables are %Transmittance, Globule Size and % Drug Diffusion. The three independent variables are

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 5 Sept - Oct 2025, pp: 389-401 www.ijprajournal.com ISSN: 2456-4494

Concentration of Oil, Concentration of Smix, and Concentration of Water.

$Y = b_1X_1+b2X2+b3X3+b12X1X2+b23X2X3 +b13X1X3+b123X1X2X3$

Y is the dependent variable and gives 7 runs and b_1 is the estimated coefficient for the factor X1.

EVALUATION PARAMETERS OF MICROEMULSION SPRAY

(1) Appearance

It was found Translucent, clear, uniform emulsion. To visualize the physical appearance of the formulation.

(2) pH

pH was measured by using pH meter. pH meter electrode was immersed into microemulsion and readings were taken at room temperature.

(3) %Transmittance

% Transmittance was measured to determine transparency of microemulsion.

Microemulsion was diluted for 100 times. % Transmittance was determined by UV- Visible spectrophotometer at 650 nm using water as blank.

(4) Viscosity

Viscosity measurement was conducted to determine the rheological characteristics of the microemulsion. Viscosity was measured by Brookfield viscometer using spindle no.61. and it was rotated on 100 rpm.

Microemulsion was placed within the beaker and spindle was submerged into it. Viscosity was measured.

(5) Dilution Test

If water is introduced into microemulsion, it will maintain its homogenous state without separating into two distinct phases and will remain clear. Microemulsion was diluted for 100 times and visually examined for clarity and phase separation.

(6) Centrifugation

This test is done for to evaluate physical stability. Centrifugation of microemulsion at 5000 rpm for 10 min is done for to study phase separation.

(7) % Drug Content

1 ml of microemulsion was transferred into a 10 ml volumetric flask and then diluted with methanol to reach a final volume of 10 ml. Methanol was taken as flask solution and absorbance was taken at 250 nm using a UV/VIS spectrophotometer after appropriate dilution.

(8) Polydispersibility Index

A measure of the distribution of molecular mass in a given polymer sample. PDI equals to 1, indicates a narrow distribution, and PDI less than 1 indicates a broader distribution.

(9) Spray pattern

A sample of 10ml from each formulation is separately weighed into a spray bottle. Subsequently, a certain amount of a dye was added to the bottles, and it is stirred using magnetic stirrer at 500rpm for 45min. A white plate was horizontally positioned 15cm away from the bottle, and spray process is conducted five times for each sample. After the process, the diameter of the spray area on the plate was measured.

(10) Globule Size

Globule Size are important characteristics of microemulsion. Small Globule Size is preferred for microemulsion. As it increases penetration across the skin.

Malvern Zeta sizer was used for measurement of globule size. Microemulsion was diluted with water. Then sample was placed in square glass cuvettes and Globule Size were measured by dynamic light scattering method.

(11) % In Vitro drug release study

Franz-diffusion cell was used for drug release study of microemulsion. Franz diffusion cell consists of donor compartment and receptor compartment. Receptor compartment was filled with pH 6.8 phosphate buffer and it was under continuous stirring and 37±1ºC temperature was maintained. Membrane was clamped between donor and receptor compartment. 1 ml of microemulsion was administered onto the membrane. 1 ml sample was taken from receptor compartment at regular interval and volume was made up with the equal volume of pH 6.8 phosphate buffer for maintenance of sink condition. Then concentration of Roflumilast is measured by UV Spectrophotometer.

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 5 Sept - Oct 2025, pp: 389-401 www.ijprajournal.com ISSN: 2456-4494

EVALUATION PARAMETERS OF OPTIMIZED MICROEMULSION SPRAY

(1) Spray Volume

The Microemulsion is filled in an aerosol bottle, Spray the microemulsion in a measuring cylinder to know the accurate quantity of microemulsion which is released by each spray.

(2) Spray Drug Content

We found the volume of microemulsion, the specific volume per spray is taken for the determination of drug content. Then the drug content per spray is to be measured under UV spectrophotometer.

(3) Zeta Potential

Zeta potential refers to the electric potential difference that exists within the interfacial layer surrounding a dispersed Globule Size or droplet, compared to a point located within the continuous phase. The zeta potential of microemulsion was determined using instruments like the Malvern Analytical.

Microemulsions with significantly higher zeta potentials, whether positive or negative, remain electrically stabilized, inhibiting coagulation or flocculation, while those with lower zeta potentials are prone to aggregation, risking physical instability.

(4) Stability Study

Stability study was conducted according to ICH guidelines under accelerated condition (40±2ºC & 75±5% relative humidity) for 1 months and emulsion spray was tested for physical and chemical stability.

II. RESULT AND DISCUSSION

2.1 Preformulation study of drug

(1) Organoleptic characteristic of drug- White, odorless and non-hygroscopic free flowing powder observed.

(2) Melting point of drug- Melting point of Roflumilast was observed same as the standard melting point so it can confirm the identification of Roflumilast.

(3) FT-IR study of Drug- FT-IR spectra of Roflumilast showed all functional group peaks present in its structure. So, its identification of drug Roflumilast ais confirmed by FT-IR.

(4) Spectrometric Analysis of Roflumilast- Maximum absorbance (λmax) was obtained at 250 nm in methanol. R^2 value observed was 0.991 with slope of regression line 0.0241 and intercept of regression line 0.0303. So, linearity was observed between range 5-30 mcg/ml.

(5) Qualitative and Quantitative estimation of Roflumilast through UV spectroscopy in phosphate buffer pH 6.8- Maximum absorbance (λmax) was obtained at 250 nm in 6.8 phosphate buffer. R^2 value observed was 0.991 with slope of regression line 0.0241 and intercept of regression line 0.0303. So, linearity was observed between range 5-30 mcg/ml.

(6) Solubility Study- Solubility study of Roflumilast was conducted in various Oils, Surfactants and Co-Surfactants for the formulation of microemulsion. In which Capryol 90 (64.95±0.58 mg/ml), Tween 80 (90.20±0.71 mg/ml) and Polyethylene glycol 400(46.98±0.26mg/ml) demonstrated highest solubility of Roflumilast. So, they were further selected as Oil, Surfactant and Co-Surfactant respectively for the preparation of microemulsion.

(7) Drug Excipients Compatibilty Study- it was concluded that there is no introduction of any new peak and removal of any peak in the functional group region of spectra. So, the drug excipients are said to be compatible with each other.

(8) Pseudoternary Phase Diagram- The bluish area indicates the possible combination of oil, Smix and water to form a microemulsion, From the above Pseudoternary phase diagrams, it was concluded that the highest microemulsion region was found in Smix ratio 3:1 compared to 1:1, 2:1, 1:2 and 1:3. So, there ratios are selected for further studies.

EVALUATION PARAMETERS OF MICROEMULSION SPRAY

(1) Appearance

Microemulsion Spray was visually examined for colour, homogeneity and consistency.

It was found Translucent, clear, uniform emulsion. To visualize the physical appearance of the formulation.

(2) pH

Skin pH is in the range of 4-6. So, Topical preparations must also be in the pH range of 4-6.

(3) % Transmittance

%Transmittance was measured to determine transparency of microemulsion spray. It was determined by UV-Visible spectrophotometer at 650nm.

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 5 Sept - Oct 2025, pp: 389-401 www.ijprajournal.com ISSN: 2456-4494

(4) Viscosity

Viscosity measurement was conducted to determine the rheological characteristics of the microemulsion spray. It was measured by Brookfield viscometer using spindle no. 61 and it was rotated on 100 rpm.

(5) Dilution test

If water is introduced in microemulsion spray, it will maintain its homogenous state without separating into two distinct phases and it will remain clear.

Microemulsion spray was diluted for 100 times and visually examined for clarity.

Results shows that the clear solution was obtained.

(6) Centrifugation

This test is done to evaluate physical stability. Centrifugation of microemulsion spray at 5000rpm for 10mins was done to study Phase Separation.

No Phase Separation was seen in all the batches.

(7) % Drug Content

1 ml of microemulsion spray was transferred into a 10 ml volumetric flask and diluted with methanol to reach a final volume of 10 ml. Methanol was taken as flask solution and absorbance was taken at 250 nm using a UV spectrophotometer after appropriate dilution.

(8) Spray Pattern

By using blue colored dye, Spray Pattern test was conducted by using all 7 batches.

(9) Globule Size- Globule Size was determined by zeta sizer, in order to know the Globule Size of microemulsion. Globule Size and polydispersity index of ME 5 was measured using Malvern Zeta sizer and the result was recorded in nm as shown in the following Figure. The particle size distribution spectra of Roflumilast diluted with water.

(10) Experimental Design Summary- The regression coefficient and p-value of the complete design were calculated for %Transmittance, Globule size and % Drug Diffusion. P-value less than 0.05 indicates the significance of the factor.

Optimization using Simplex Lattice design:

Microemulsion was optimized by using Simplex lattice design. Responses of all the design batches are presented in table.

Effect of independent variables on Y1 (Transmittance):

Anova table shows the p-value less than 0.05 which indicates that the model is significant. We can conclude that Response Y1 %Transmittance was analyzed using a linear model through Design Expert 13.5 software.

As per above equation its so that concentration of Smix give more effect on % transmittance as compare to oil and water. As we increase the concentration of Smix % transmittance increases.

Full model:- 91.9779(X1) +98.3579(X2) +94.4499(X3) +11.4239(X1) (X2) +13.4639(X1) (X3) +(-5.09606) (X2) (X3)

Reduced model:- 91.9779(X1) +98.3579(X2) +94.4499(X3) +11.4239(X1) (X2) +13.4639(X1) (X3)

Effect of independent variables on Y2 (Globule Size):

The p-value is 0.0019 which is less than 0.05, So the model is significant.

➢ Linear Model is used for analysis

➢ As we can conclude from Contour plot and 3-D surface plot that the increase concentration of Oils gives more effect on globule size as compare to smix and water. As increase in concentration of oil globule size of formulation increase.

Full model:- 420.116(X1) +149.3316(X2) +198.996(X3)

Reduced model:- 420.116(X1) +149.3316(X2)

Effect of independent variables on Y3 (Drug Diffusion):

Here, p-value is 0.0489, which is less than 0.05, that's why the model is significant. It is the Quadratic model. From Contour plot and 3-D surface graph, we can say that Concentration of Oil, Smix and Water gives positive effect to % Drug diffusion.

Full model:- 91.6955(X1) +94.6955(X2) +95.4255(X3) +18.3309(X1) (X2) +19.0309(X1) (X3) + (-9.00909) (X2) (X3)

Reduced model:- 91.6955(X1) +94.6955(X2) +95.4255(X3) +18.3309(X1) (X2) +19.0309(X1) (X3)

Optimization of formulation:

ME5 batch containing 10% Capryol 90, 35% Smix and 55% Water in 3:1 ratio of Tween 80: Polyethylene glycol 400 was optimized because

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 5 Sept - Oct 2025, pp: 389-401 www.ijprajournal.com ISSN: 2456-4494

it showed highest 97.89% Transmittance, 154.1nm Globule Size and 98.38 % Drug Diffusion and good PDI 0.244.

Stability study of optimized batch:

Stability study of microemulsion spray was conducted for one month. All the parameters of microemulsion spray were evaluated before and after the one month. They were almost similar. So prepared microemulsion spray was stable in stability study.

III. CONCLUSION:

The present research work aimed to formulate topical microemulsion spray of Roflumilast for the treatment of psoriasis. Roflumilast is a selective phosphodiesterase-4 inhibitor. Which is used for treatment of chronic obstructive pulmonary disease (COPD) and psoriasis. Microemulsion spray is a combination of microemulsion and spray. It gives the advantages of both dosage form. Microemulsion increases the penetration and spray prolongs the contact time to the skin with ease of application. Microemulsion is less sticky, easily spreadable and exhibits superior stability compared to cream, lotion and ointment. Spectrometric analysis of Roflumilast in methanol and phosphate buffer pH 6.8 was done by using UV-Visible spectrophotometer and λmax was obtained at 250 nm respectively. Identification of drug was done by Fourier transform infrared spectroscopy. Solubility study was carried out to find suitable Oil, Surfactant and Co-Surfactant. In solubility study, Capryol 90 (54.29), Tween 80 (90.13) and Polyethylene glycol 400 (29.75) demonstrated highest solubility of Roflumilast. So, they were further selected as Oil, Surfactant and Co-Surfactant respectively for the preparation of microemulsion. Drug-Excipients compatibility study was conducted by Fourier transform infrared spectroscopy. In which there was no interaction of any kind. Pseudo Ternary Phase Diagrams for different Smix ratios were constructed. In which, Smix3:1 showed highest microemulsion region compared to 2:1,1:1,1:2 and 1:3. So it was further selected for preparation of microemulsion. Simplex Lattice design was applied for optimization of Roflumilast microemulsion. Concentration of Oil (X1), Concentration of Smix (X2) and Concentration of Water (X3) were chosen as independent variables, while % Transmittance (Y1), Globule Size nm (Y2) and % Drug Diffusion (Y3) were selected as dependent variables. 7 batches were formulated and evaluated for various parameters and statistical analysis of dependent variables were done. Optimized Roflumilast ME5 was transferred into a spray bottle and Roflumilast spray was formulated. Prepared microemulsion spray has excellent homogeneity, with pH 5.8, good consistency, and skin compatible. In vitro drug release study was carried out by using Franz diffusion cell and it demonstrated 98.58 % drug diffusion. It is concluded that topical microemulsion spray of Roflumilast can be effectively used for treatment of psoriasis.

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International Journal of Pharmaceutical Research and Applications
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TABLES & FIGURES

Table 1 - Formulation of Simplex Lattice design batches

Ingredients (%)	ME1	ME2	ME3	ME4	ME5	ME6	ME7
Roflumilast	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Capryol 90	10	20	10	15	10	15	33
Tween 80	20	20	26.67	20	23.33	23.33	22
Polyethylene glycol 400	10	10	13.3	10	11.6	11.67	11
Methyl paraben	0.15	0.15	0.15	0.15	0.15	0.15	0.15
Water	60	50	50	55	55	50	33.34

Table 2 – Evaluation parameters of Roflumilast Microemulsion spray

Formulation Code	pH	%Transmittance	Polydispersibility Index	Centrifugation	Viscosity	%Drug content
ME1	5.9±0.03	94.72±0.02	0.658	No phase separation found	112.53±0.06	99.54±0.68
ME2	6.3±0.01	90.68±0.01	0.490	No phase separation found	108.56±0.07	98.37±0.55
ME3	6.2±0.02	94.45±0.04	0.155	No phase separation found	108.93±0.04	97.17±0.52
ME4	6.4±0.07	95.45±0.02	0.177	No phase separation found	106.58±0.02	98.83±0.94
ME5	5.8±0.04	97.89±0.07	0.244	No phase separation found	105.98±0.11	99.63±0.42
ME6	5.6±0.01	91.23±0.08	0.740	No phase separation found	109.29±0.07	97.72±0.61
ME7	6.2±0.01	95.56±0.03	0.254	No phase separation found	120.89±0.05	99.36±0.11

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 5 Sept - Oct 2025, pp: 389-401 www.ijprajournal.com ISSN: 2456-4494

Table 3 – In vitro drug release data

Sr. No	Time (min)	ME1	ME2	ME3	ME4	ME5	ME6	ME7
1	**30**	16.65	16.47	14.27	12.94	17.54	13.64	14.53
2	**60**	25.94	27.54	22.94	22.81	29.67	24.65	22.16
3	**120**	43.27	44.61	40.82	39.62	45.23	40.24	35.67
4	**180**	55.92	56.64	52.84	47.45	57.94	53.55	51.25
5	**240**	70.41	70.05	69.84	63.95	72.18	61.85	69.82
6	**300**	83.19	84.67	81.45	75.94	85.94	76.34	74.27
7	**360**	92.47	91.34	91.68	88.92	96.88	89.84	87.66

Table 4 - Simplex Lattice design batches & its responses

Formulation Code	X1 (Concentration of Oil) (%)	X2 (Concentration of Smix) (%)	X3 (Concentration of water) (%)	Y1 (%Transmittance)	Y2 (Globule Size)	Y3 (% Drug Diffusion)
ME1	10	30	60	94.72	401.2	91.68
ME2	20	30	50	90.68	195.2	94.68
ME3	10	40	50	94.45	334.5	95.41
ME4	15	30	55	95.45	307.1	97.84
ME5	10	35	55	97.89	154.1	98.38
ME6	15	35	50	91.23	165.7	92.87
ME7	33.33	33.33	33.34	95.56	241.9	96.95

Table 5 - In vitro drug release

Sr. No.	Evaluation parameter	Result	After 1 month
1	Color	Translucent	Translucent
2	Homogeneity	Excellent	Excellent
3	Consistency	Good	Good
4	pH	5.9	5.8
5	Viscosity	105.98	105.95
6	Centrifugation	No phase Separation seen	No phase Separation seen
7	%Transmittance	97.89%	97.08%
8	% Drug Diffusion	98.38%	98.11%
9	%Drug release at 6 hr	96.88%	96.78%
10	% Drug Content	99.63%	99.62%
11	Spray Volume	0.35ml	0.35ml
12	1 Spray drug Content	1.05mg	1.05mg

Table 6 - % In Vitro drug release of Roflumilast microemulsions

Sr. No	Time (min)	ME1	ME2	ME3	ME4	ME5	ME6	ME7
1	**30**	16.65	16.47	14.27	12.94	17.54	13.64	14.53
2	**60**	25.94	27.54	22.94	22.81	29.67	24.65	22.16
3	**120**	43.27	44.61	40.82	39.62	45.23	40.24	35.67
4	**180**	55.92	56.64	52.84	47.45	57.94	53.55	51.25
5	**240**	70.41	70.05	69.84	63.95	72.18	61.85	69.82
6	**300**	83.19	84.67	81.45	75.94	85.94	76.34	74.27
7	**360**	92.47	91.34	91.68	88.92	96.88	89.84	87.66

International Journal of Pharmaceutical Research and Applications
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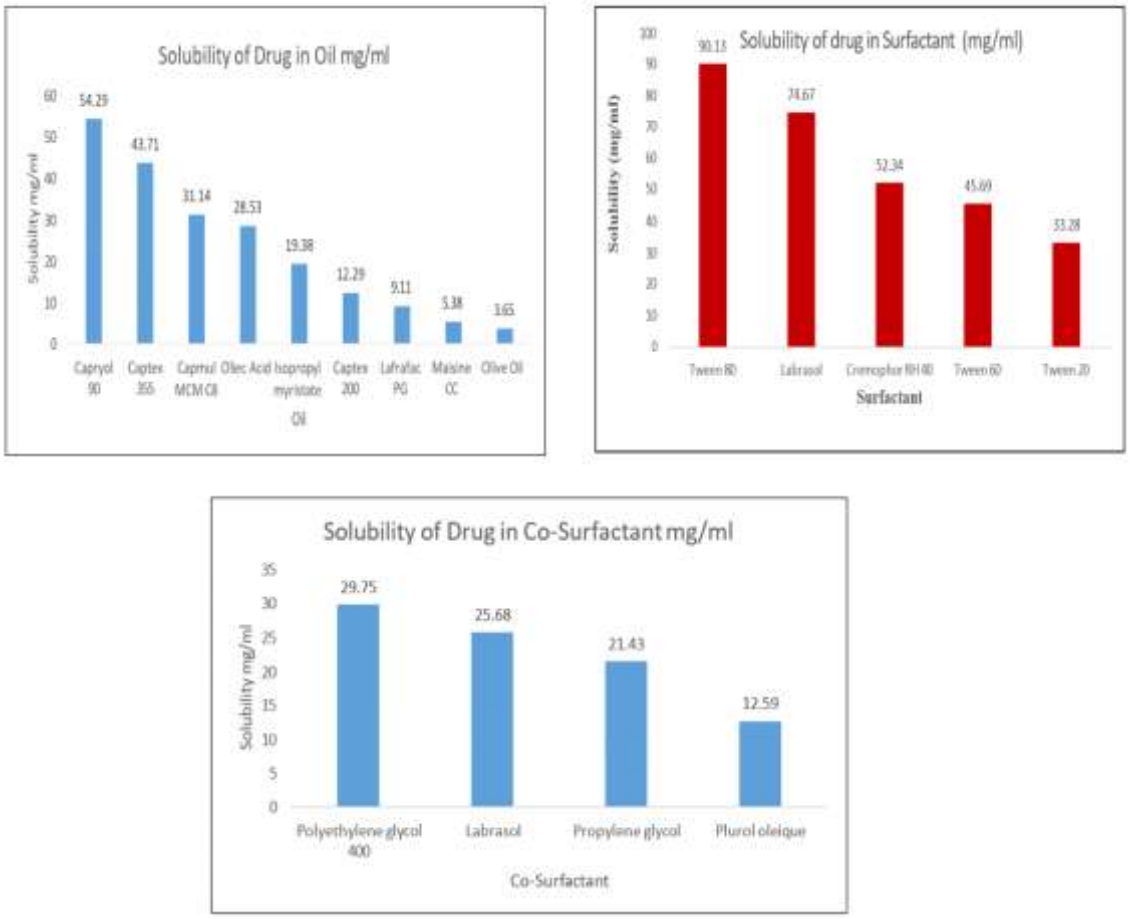

Figure 1 – Solubility of Roflumilast in various oils, surfactants and co- surfactants

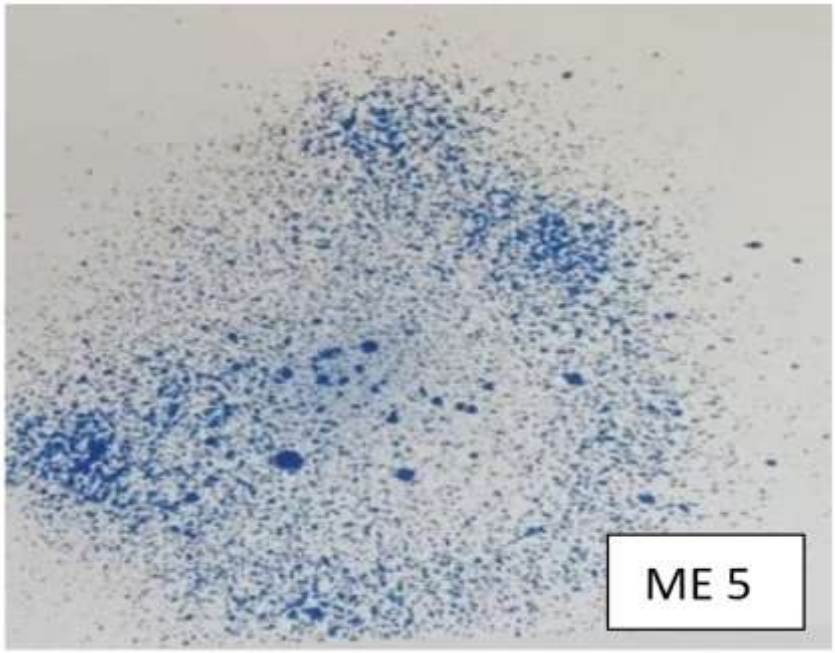

Figure 2- Spray pattern

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 5 Sept - Oct 2025, pp: 389-401 www.ijprajournal.com ISSN: 2456-4494

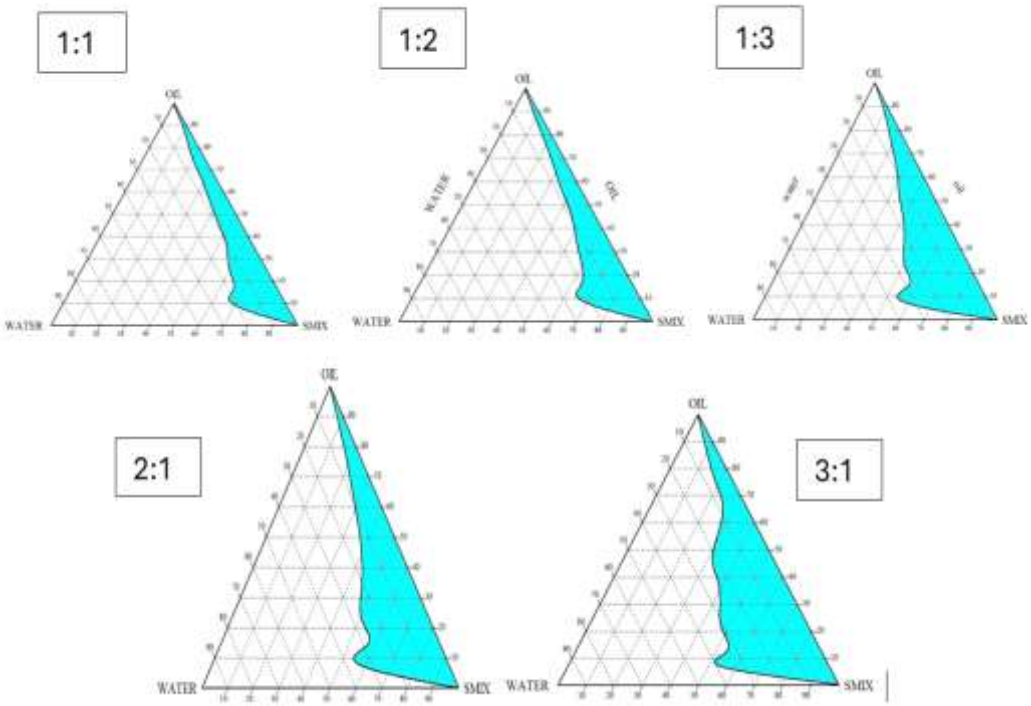

Figure 3- Pseudo ternary Phase Diagram

Results

		Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm): 154.1	Peak 1:	181.4	97.4	74.49
PdI: 0.244	Peak 2:	4672	2.6	794.4
Intercept: 0.860	Peak 3:	0.000	0.0	0.000

Result quality : Good

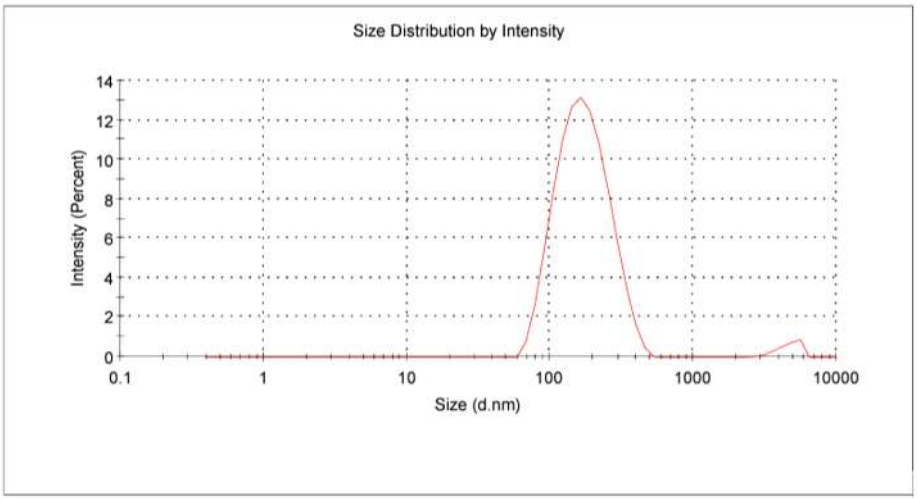

Figure 4- Globule Size

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 5 Sept - Oct 2025, pp: 389-401 www.ijprajournal.com ISSN: 2456-4494

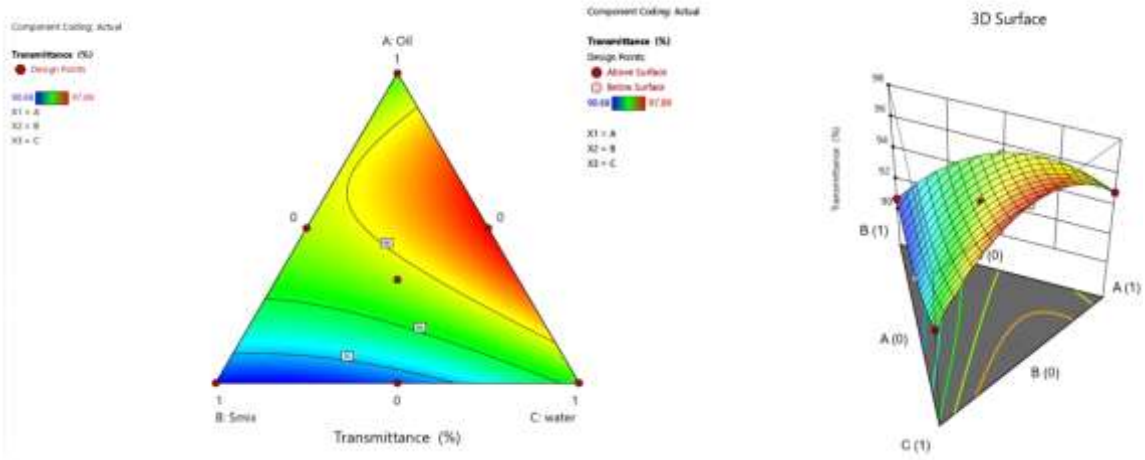

Figure 5– Contour plot and response surface plot for response Y1 (Transmittance)

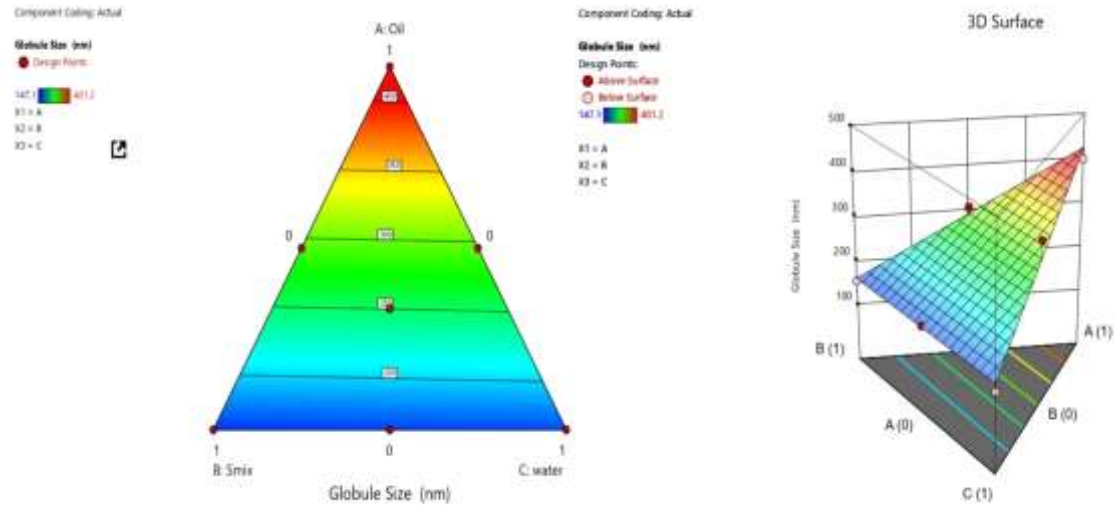

Figure 6– Contour plot and response surface plot for response Y2 (Globule Size)

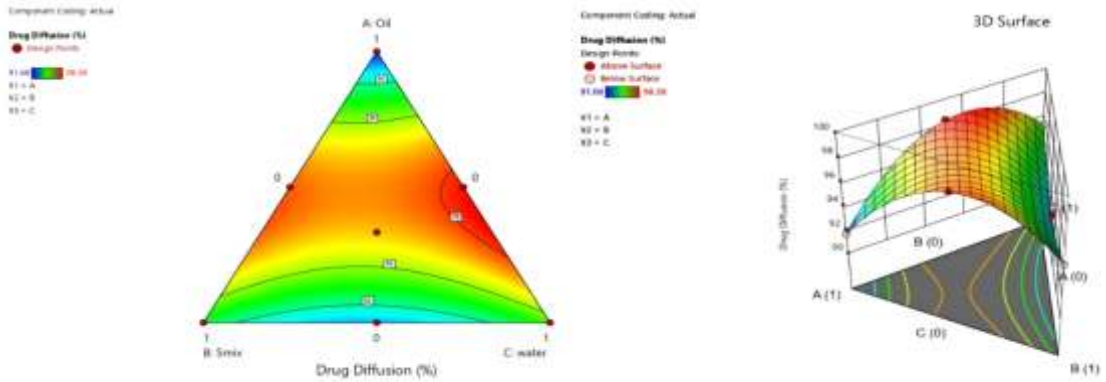

Figure 7 – Contour plot and response surface plot for response Y3 (Drug Diffusion)

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 5 Sept - Oct 2025, pp: 389-401 www.ijprajournal.com ISSN: 2456-4494

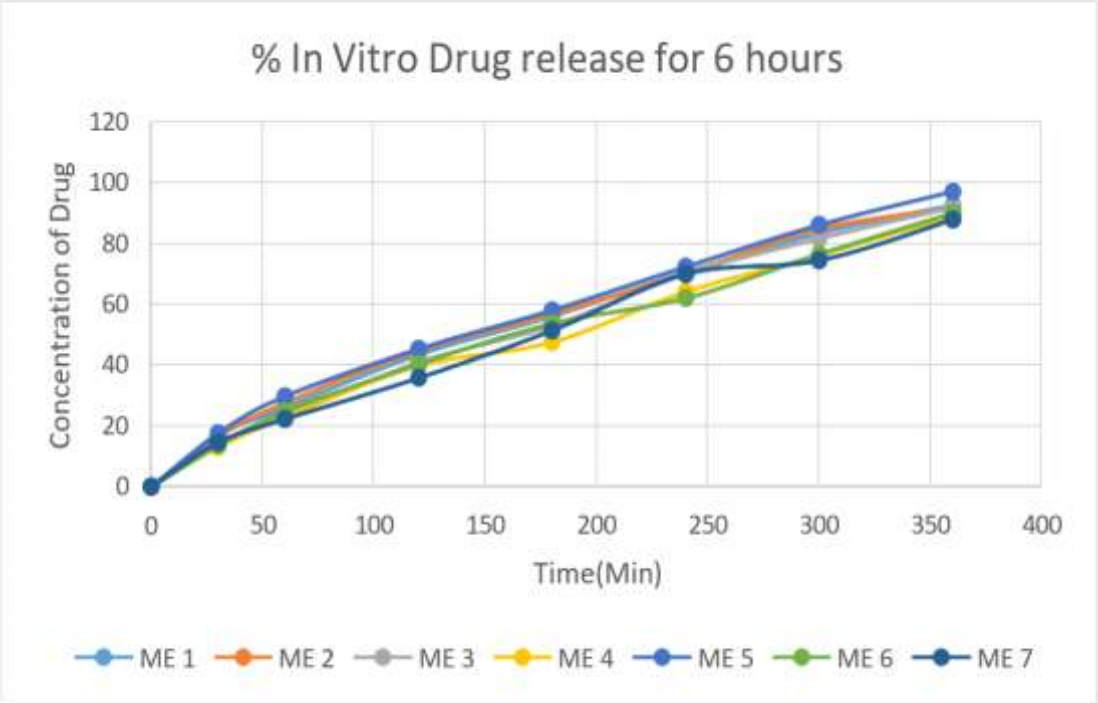

Figure 8 - % In vitro drug release of Roflumilast for all 7 batches

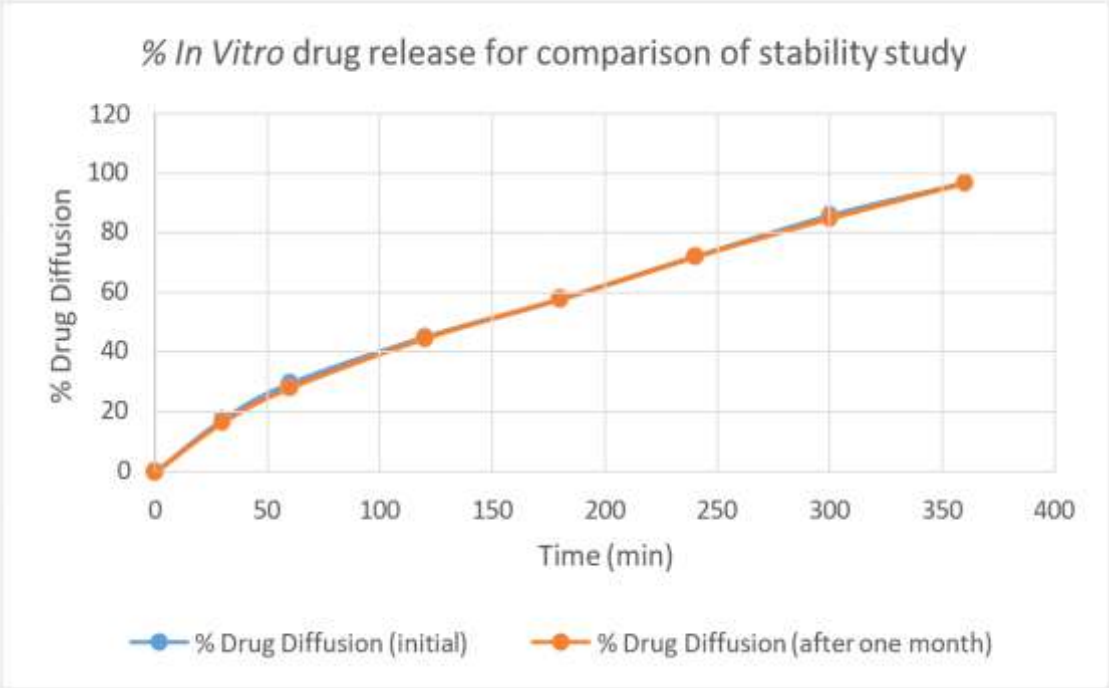

Figure 9- In vitro drug Release for comparison with stability after 1 month