Dichloromethane and methanol were obtained from Ren Chem labs, Polyvinyl alcohol were purchased from Loba Chemicals, Mumbai.

Tazarotene was received as a generous gift from Sun Pharma, New Delhi, India. All other materials and chemicals used were of either pharmaceutical or analytical grade.

Drug excipients compatibility study

Drug-Excipients interaction plays a vital role in achieving the stability of the drug in dosage form. Fourier transform infrared spectroscopy (FT-IR) was used to study the physical and chemical interactions between drug and excipients. FT-IR spectra of Tazarotene, Eudragit RS-100 and Mixture (Tazarotene and Eudragit RS-100) were recorded using KBr mixing method on FT-IR instrument (FTIR-1700, Shimadzu, Kyoto, Japan) [6, 7].

Preliminary screening of formulation parameters and development of tazarotene microsponge

Preliminary trial of tazarotene microsponge was done by selecting parameters such as polymer conc., Speed and PVA concentration on % drug entrapment, % yield, drug content and mean particle size. Tazarotene microsponge was prepared by a quasi- emulation solvent diffusion method. In this method internal phase was prepared by dissolving required amount of tazarotene and polymer (Eudragit RS-100, Eudragit RL-100, Ethyl Cellulose) in 100 ml dichloromethane and 8 ml methanol at 60 °C. External phase was prepared by dissolving 0.5% and 1% polyvinyl alcohol (PVA) in distilled water as shown in table 1. Internal phase was gradually added into external phase at 500 rpm, 1000 rpm and 1500 rpm with help of Magnetic Stirrer (REMI Equipment, India). After emulsification, the mixture was continuously stirred for 3 h. Then, the mixture was filtered and separates the microsponges. This prepared microsponge was washed with distilled water and dried by hot air oven at 40 °C for 24 h. All the batches were stored properly and evaluation was carried out [8, 9].

Evaluation parameters of tazarotene microsponge

Particle size analysis: Particle size analysis of tazarotene microsponge was analyzed by optical microscopy method, using calibrated eye piece and stage micrometer slide.
% Yield: The % yield of the tazarotene loaded microsponge can be determined by the following equation:

\[
\text{Production yield} = \frac{\text{Practical Mass of Microsponges}}{\text{Theoretical Mass (Polymer+ Drug)}} \times 100
\]

% Drug entrapment: The % Drug entrapment of the microsponges can be calculated according to the following equation:

\[
\% \text{ Drug entrapment} = \frac{\text{Actual Drug Content in microsponges}}{\text{Theoretical Drug Content}} \times 100
\]

Morphology and Surface topography: Developed tazarotene microsponge coated with gold-palladium under an argon atmosphere at room temperature and surface morphology studied by scanning electron microscopy (SEM). Fractured microsponge SEM was also taken to illustrate its ultra-structure [10, 11].

Drug content: 100 mg of tazarotene microsponge dissolved in methanol and phosphate buffer solution pH 7.4 and allowed to stand for 24 h. The solution was filtered through whatman filter paper (No.41) and drug content was analyzed spectrophotometrically (Shimadzu 1700) at 350 nm, against standard methanolic and phosphate buffer solution pH 7.4.

In vitro dissolution study for the time required to 80% drug release: The dissolution profile of tazarotene microsponges studied by use of USP Type-I dissolution apparatus with a modified basket consisted of 5μm stainless steel mesh. A sample equivalent to 100 mg of tazarotene nitrate was taken in the basket. The 100 rpm and temperature of 37±0.5°C were maintained throughout the experiment. The dissolution medium (900 ml) is phosphate buffer pH 7.4 while considering solubility of actives to ensure sink conditions. At fixed intervals, aliquots were withdrawn and replaced with fresh dissolution medium. Samples from the dissolution medium can be analysed by UV spectrophotometer (Shimadzu 1700) at 350 nm at specific time intervals (1, 2, 3, 4, 5, 6, 7, and 8 hour). The concentration of drug released at different time intervals was determined by measuring absorbance [12, 13].

Optimization of tazarotene microsponge by 3^2 full factorial design

A 3^2 full factorial design was employed in the present study. In this design 2 factors were evaluated, each at 3 levels and experimental trials was performed for all 9 possible combinations. Preliminary Screening Two variables, the concentration of Polymer and concentration of PVA were found critical. So, they were optimized using different trials, while other parameters were kept constant. On the basis of preliminary results, concentration of Polymer (X_1) and concentration of PVA (X_2) were chosen as independent variables in 3^2 full factorial design, while Particle Size (Y_1), % Drug entrapment (Y_2). Time required to 80% drug release (Y_3) was selected as dependent variables. Multiple linear regression analysis, ANOVA and graphical representation of the influence of factor by 3D plots were performed using sigma plot software 11.0. The experimental runs and measured responses of 3^2 factorial design of batches of tazarotene microsponge depleted in table 2 [14, 15].

Development of 0.1% tazarotene microsponge topical gel

The topical gel was developed by dissolving 3% w/w HPMC K100 M in a sufficient amount of pH 7.4 citrate phosphate buffer. Gel was kept overnight to remove air bubble and add benzyl alcohol (1% v/v) as a preservative. Then, add a tazarotene microsponge (0.1 %w/w) to gel with geometric dilution [16, 17].

Evaluation of 0.1 % tazarotene microsponge topical gel

Viscosity: The viscosity of the gel was determined by Brookfield Viscometer (Model-LVDV-E). It was determined using with spindle no. 64 at 100 rpm at temperature 25°C. Rotate the spindle in the microsponge gel till get a constant dial reading.

pH: The pH of gel was determined by a digital pH meter. One gram of gel was dissolved in 100 ml distilled water and stored for 2 hr. Then, electrode was the dipped into gel for 30 min until constant reading obtained.

Drug content: 1 gm of microsponge gel was accurately weighed and dissolved in pH 7.4 citrate phosphate buffer using sonicator. A sample from this aliquot was analyzed by UV spectrophotometer (Shimadzu 1700) at 350 nm [18, 19].

Spreadability: Spreadability apparatus consists of a wooden block with a ground glass plate (20X20) fixed on to it. A pre-determined amount of gel was placed on ground glass plate and it was sandwich with another glass plate. Accurately 500 gm weight was placed on the top of the two glass plate to expel the air and provide a uniform film of the gel between the plates. Excess of gel was wiped off. The top plate was subjected to a put 10 gm weight and allows slipping the plate. The spreadability was calculated by using the following equation.

\[
S = ML/T
\]

Where, S = spreadability M = weight on top plate (10 gms) L= length of the glass plate, T=time taken to separate the plate completely from each other.

In-vitro diffusion study: The release from the gels was examined through a cellophane membrane using a modified Franz diffusion cell. Prior to study, the cellophane membrane was soaked in diffusion medium for 4 hr and then placed on diffusion cell assembly. An aqueous solution of citrate phosphate buffer pH 7.4 was used as the receptor medium and 1 gm of the test gel was placed on the donor side. The receptor medium was kept at 37±0.5 °C. At predetermined time intervals, sample was taken from the receptor compartment and replaced with the fresh citrate phosphate buffer pH 7.4. Absorbance of the solutions was measured spectrophotometrically (Shimadzu 1700) at 350 nm [20, 21].

Kinetic Modelling of Dissolution Data: In order to understand the kinetics and release mechanisms of drug, the result of in vitro diffusion study of gel was fitted in with various kinetics models like zero order, first order, Higuchi model and Korsmeyer Peppas model. The linearity of the plots was obtained from the value of regression co-efficient (R). The model with the highest linearity (R^2 value) was chosen as the Best-fit kinetic model [22, 23].

Photostability study: Prepared 0.1% tazarotene microsponge containing gel was filled in clear polypropylene syringes, one for test and other for control. It was assayed by UV spectrophotometry immediately after preparation and analysed the drug content. This study was carrying out for measurement of initial concentration. Then same tazarotene microsponge containing gel (0.1%) were exposed to UV light with an integrated intensity from 352 nm of 22 watt/m for 8 h. This spectral region was selected to provide a more energetic exposure than visible light and is consistent with the International Conference on Harmonization (ICH) guidelines for photostability testing [24].

RESULTS AND DISCUSSION

Drug excipients compatibility study

Fourier transform infrared spectroscopy (FT-IR) was used to study the physical and chemical interactions between drug and excipients. FT-IR spectra of tazarotene and mixture of tazarotene with eudragit RS-100 were recorded using KBr mixing method on FT-IR instrument. The drug exhibited peaks due to amide group, alcohol group and C-H, C=O, C-C stretching. It was observed that there were no very minor changes in drug main peaks in the IR spectra of the mixture and pure drug. The FTIR study revealed no physical or chemical interaction of tazarotene with eudragit RS-100 [25].

Preliminary screening of formulation parameters

Preliminary trial of tazarotene microsponge result was shown in table 1. Good % of yield and mean particle size observed in batch T-1 which containing eudragit RS-100. Stickiness was detecting in batch T-2 which containing eudragit RL-100. Particle size found uneven when we use ethyl cellulose in batch T-3. HPMC K4M was separate out from the solvent in batch T-4. So, further investigation was using with eudragit RS-100. Uneven particle size was observed in batch T-5 and T-7. So, 1000 rpm was selected for further Preliminary trial batch. Batch T-8 was given a higher % of yield compare to batch T-9. The results of preliminary study revealed that eudragit RS100 and PVA both required achieving the desired release profile. Hence, further trials were carried out using various combinations eudragit RS100 and PVA in order to understand their effect and to optimize concentration of both for desired release profile.
Polynomial terms (X^12 and X^22) are included to investigate the result of changing one factor at a time from its low to high value. Where, Y is the dependent variable, b_0 is the arithmetic mean of all runs, b_i are the estimated coefficients for the related factor X_i. The main effects (X_1 and X_2) represent the average response of the 9 runs and any b_i is the estimated coefficients for the interaction term X_iX_j shows how the response changes when the two factors change simultaneously. Evaluation data for tazarotene microsponge was presented in Table 2.

A statistical model incorporating interactive and polynomial terms was used to evaluate the responses:

\[ Y = b_0 + b_{11}X_1 + b_{22}X_2 + b_{12}X_1X_2 \]

where, Y is the dependent variable, b_0 is the arithmetic mean of all runs, b_{11}, b_{22}, and b_{12} are the estimated coefficients for the main effect of X_1, X_2, and the interaction term X_1X_2 respectively.

### Table 1: Evaluation of preliminary screening batch of tazarotene microsponge

| Batch | Polymer | Speed (RPM) | PVA Conc. (%) | % Yield | % Drug entrapment | Particle size (µm) | Time required to 80% drug release |
|-------|---------|-------------|---------------|---------|-------------------|-------------------|----------------------------------|
| T-1   | 0.1% Eudragit RS100 | 1000         | 0.5           | 68.5±1.75 | 67.6±1.12         | 70±4             | 360±4     |
| T-2   | 0.1% Eudragit RL100 | 1000         | 0.5           | 77.2±2.45 | 63.4±2.78         | 45±5             | 350±3     |
| T-3   | 0.1% Ethyl cellulose| 1000         | 0.5           | 62.5±0.89 | 55.9±0.36         | 57±1             | 310±5     |
| T-4   | 0.1% HPMC K4M       | 1000         | 0.5           | -        | -                 | -                | -        |
| T-5   | 0.1% Eudragit RS100 | 500          | 0.5           | 71.2±2.56 | 66.9±0.78         | 77±6             | 340±5     |
| T-6   | 0.1% Eudragit RS100 | 1000         | 0.5           | 76.0±1.13 | 72.2±0.34         | 20±2             | 390±5     |
| T-7   | 0.1% Eudragit RS100 | 1500         | 0.5           | 87.9±1.07 | 72.0±1.78         | 15±4             | 440±3     |
| T-8   | 0.1% Eudragit RS100 | 1000         | 0.5           | 74.0±0.56 | 67.2±0.67         | 15±4             | 400±2     |
| T-9   | 0.1% Eudragit RS100 | 1000         | 1.0           | 43.1±2.23 | 42.0±1.25         | 71±6             | 320±4     |

n=6

### Table 2: Runs and measured responses of 3^2 factorial design for tazarotene microsponge

| Batch code | % of Eudragit RS-100(X_1) | Concentration of PVA (X_2) | Particle size (µm) (Y_1) | % Drug entrapment (Y_2) | Time required to 80% drug release (Y_3) |
|------------|---------------------------|---------------------------|--------------------------|-------------------------|----------------------------------------|
| F1         | -1                        | -1                        | 158±2                    | 73.2±2.34               | 390±4                                  |
| F2         | -1                        | 0                         | 180±5                    | 74.95±0.82              | 415±1                                  |
| F3         | -1                        | 1                         | 196±2                    | 66.7±0.11               | 430±5                                  |
| F4         | 0                         | -1                        | 193±5                    | 77.8±2.31               | 380±1                                  |
| F5         | 0                         | 0                         | 204±4                    | 89.19±1.09              | 415±3                                  |
| F6         | 0                         | 1                         | 227±2                    | 75.46±0.86              | 420±6                                  |
| F7         | 1                         | -1                        | 213±4                    | 72.09±1.34              | 435±2                                  |
| F8         | 1                         | 0                         | 226±3                    | 84.67±2.51              | 440±5                                  |
| F9         | 1                         | 1                         | 230±2                    | 70.93±0.88              | 445±3                                  |

Factors and the levels in the design:

- Independent variables:
  - Low (-1)
  - Medium (0)
  - High (1)

- % of Eudragit RS100(X_1):
  - 0.05
  - 0.1
  - 0.15
- % of PVA (X_2):
  - 0.25
  - 0.50
  - 0.75

**Full and reduced model for particle size**

\[ \text{Particle size} = 207.444 + (23.833 * X_1) + (16.167 * X_2) - (6.167 * X_1^2) + (0.833 * X_2^2) + (3.250 * X_1 * X_2) \]

From the 3D plot (Fig. 3) and the regression coefficient values of factors, it was concluded that when % of eudragit RS-100 and % of PVA was increased that time particle size also increase and it’s lead to more drug entrapment. The results also indicated that the eudragit RS-100 was given a more significant impact on particle size. Both the eudragit RS-100 and % of PVA showed significant effect in the model. Interaction and nonlinearity were not observed. For particle size, the significant levels of the coefficients b_1, b_2, and b_12 were
found to be P= 0.073, 0.738 and 0.136 respectively, so they were omitted from the full model to generate a reduced model. The coefficients b1 and b2 were found to be significant at P<0.05; hence, it was retained in the reduced model. SEM of tazarotene microsponge was shown in fig. 6. The reduced model for Particle Size,

\[ \text{Particle Size} = 207.444 + (23.833 \times X_1) + (16.167 \times X_2) \]

Fig. 3: 3D plot showing the effect of % of eudragit RS-100(X1) and PVA (X2) on particle size (Y1)

Fig. 4: 3D plot showing the effect of eudragit RS-100(X1) and PVA (X2) on % of drug entrapment (Y2)

Fig. 5: 3D plot showing the effect of eudragit RS-100(X1) and PVA (X2) on time required to 80% drug release

Fig. 6: SEM of tazarotene microsponge

Full and reduced model for % of drug entrapment

\[ \% \text{ Drug entrapment} = 86.754 + (3.473 \times X_1) - (0.333 \times X_2) - (5.727 \times X_1^2) - (8.907 \times X_2^2) + (3.335 \times X_1 \times X_2) \]

From the 3D plot (fig. 4) and the regression coefficient values of factors, it was concluded that corresponding increase in the % drug entrapment of microsponge was observed with increase in con. of eudragit RS-100. From regression, it is observed that X1 was significant model terms which affect the % of drug entrapment. Interaction and non-linearity was not observed. For % of drug entrapment, the significance levels of the co-efficients b1, b11 and b12 were found to be P = 0.779, 0.056 and 0.087, respectively. So, they were omitted from the full model to generate a reduced model. The reduced model for % drug entrapment,

\[ \% \text{Drug entrapment} = 86.754 + (3.473 \times X_1) - (8.907 \times X_2^2) \]

Interaction and non-linearity was not observed. For % of drug entrapment, the significance levels of the co-efficients b1, b11 and b12 were found to be P = 0.079, 0.056 and 0.087, respectively. So, they were omitted from the full model to generate a reduced model. The reduced model for % drug entrapment,

Interaction and non-linearity was not observed. For % of drug entrapment, the significance levels of the co-efficients b1, b11 and b12 were found to be P = 0.779, 0.056 and 0.087, respectively. So, they were omitted from the full model to generate a reduced model. The reduced model for % drug entrapment,

\[ \% \text{Drug entrapment} = 86.754 + (3.473 \times X_1) - (8.907 \times X_2^2) \]

Table 3: Summary of regression output of factors for measured responses

| Responses | Model     | Coefficient of regression parameters | R²   |
|-----------|-----------|---------------------------------------|------|
|           | b₀        | b₁         | b₂         | b₁₁        | b₁₂        |      |
| Particle Size | Full      | 207.444    | 23.833     | 16.167     | 6.167*     | 3.250* | 0.994 |
|           | Reduced   | 207.444    | 23.833     | 16.167     | -          | -      |      |
| % Drug entrapment | Full      | 86.754     | 3.473      | 0.333*     | 5.727*     | 8.907  | 3.335* | 0.942 |
|           | Reduced   | 86.754     | 3.473      | -          | 8.907      | -      |      |
| Time required to 80% drug release | Full      | 409.444    | 14.167     | 15.000     | 20.833     | 6.667* | 7.500* | 0.961 |
|           | Reduced   | 409.444    | 14.167     | 15.000     | 20.833     | -      |      |

*indicated the coefficient with p>0.05
was found 7.06±0.21 and it was indicated topical gel was safe, stable and non-irritate. The values of spreadability indicated that the gel was found 2933.33 ±12 cp. The pH of tazarotene microsponge gel was 4.15.

Time required to 80% drug release = 409.944+(14.167 X1)+(15.000 X2)+(20.833 X12) (n=6) 

From the 3D plot (fig. 5) and the regression coefficient values of factors, it was concluded that corresponding increase in the time required to 80% drug release of microsponge was observed with increase in concentration of polymer and PVA concentration. From regression it is observed that X1 and X2 were equivalent significant model terms which affect the on drug release. Interaction and nonlinearity were not observed. For time required to 80% drug release, the significance levels of the coefficients b22 and b12 were found to be P= 0.278 and 0.126 respectively. So, it was omitted from the full model to generate a reduced model. The coefficients b0, b1, and b31 were found to be significant at P<0.05; hence they were retained in the reduced model. The reduced model for time required to 80% drug release [28, 29]

= 409.444+(14.167 X1)+(15.000 X2)+(20.833 X12)

Full and reduced model for time required to 80% drug release

| Parameter          | Actual value | Predicted value |
|--------------------|--------------|-----------------|
| Particle size (µm) | 7.0±2        | 8.0±1.2         |
| % Drug entrapment  | 84.2±1.22    | 87.2±4.24       |
| Time required to 80% drug release | 403±4 | 409.943 |

(n=6)

Selection of optimized batch in the factorial design study

In the present study, the following constraints were arbitrarily used for the selection of an optimized batch: particle size<200 µm, drug entrapment>70 %, and time required to 80% drug release>360 min. Batches F1, F2, F3, and F4 met the selection criteria. Batch F1 showed lowest particle size (158 µm) and 80 % drug release in 390 min. Hence, Batch F1 was selected as an optimized batch. The optimized formulation was added into the 3% HPMC K-100M gel. [29, 30]

Evaluation of 0.1% tazarotene microsponge topical gels

The optimized tazarotene microsponge formulation batch F-1 was subjected to further characterization studies and incorporated into gel to get homogeneous based delivery systems. The gel was prepared by using 3% HPMC K-100M. The prepared gel was evaluated for physicochemical characteristics and it showed desired drug content, in vitro diffusion, spreadability, pH and viscosity as per standard criteria as shown in table 7. The gel color was white and that color was stable along the period of evaluation. The drug content was found 87.27±2.32 %. It showed a good content uniformity for the prepared microsponge. The viscosity of the gel was found 2933.33±12 cp. The pH of tazarotene microsponge gel was found 7.06±0.21 and it was indicated topical gel was safe, stable and non-irritate. The values of spreadability indicated that the gel was easily spreadable by a small amount of shear. Spreadability of tazarotenemicrosponge gel was found to be 16.98±0.5 1 gm. cm/sec indicating that spreadability of drug-loaded microsponge gel was good. The in-vitro diffusion studies were carried out for tazarotenemicrosponge gel using citrate phosphate buffer pH 7.4.

In vitro diffusion of formulation is shown in fig. 7. It was observed that the gel formulation showed a drug diffused upto 10 hr. The results indicated that the cumulative amount of drug permeated per unit skin surface area from the microsponge loaded gel formulation was 93.40% for 10 hr. To determine the kinetics of release, drug diffusion data were treated with different kinetic equations. Obtained drug diffusion data was fitted to Zero order, First order, Higuchi model and Korsmeyer-peppas model. The correlation coefficient (R) was used to study the release mechanism of tazarotenemicrosponge gel is reported in table 7. The model that gave the high R value was considered as the best fit of release data. From the result, the best fit model for tazarotenemicrosponge gel formulation is Zero order (R2= 0.987). 0.1% Tazarotene Microsponge Topical Gel was kept for photostability study to UV light with an integrated intensity from 352 nm of 22 watt/m for 8 h. Initial drug content was found 87.27±2.32 % and after 8 h drug content was 80.63±1.42 %. There is no significant difference in drug content after photostability study result shown in table 8.

| Parameter          | Actual value | Predicted value |
|--------------------|--------------|-----------------|
| Particle size (µm) | 7.0±2        | 8.0±1.2         |
| % Drug entrapment  | 84.2±1.22    | 87.2±4.24       |
| Time required to 80% drug release | 403±4 | 409.943 |

(n=6)
Table 7: Evaluation of 0.1% tazarotene microsponge topical gel

| Parameter         | Topical gel          |
|-------------------|----------------------|
| Viscosity         | 2933.33±12.56 cp     |
| pH                | 7.06±0.21            |
| Spreadability     | 16.9±0.51 gm. cm/sec |
| Drug content      | 87.27±2.32 %         |
| Zero order R²     | 0.987                |
| First order R²    | 0.939                |
| Higuchi model R²  | 0.985                |
| Korsmeyer-peppas model R² | 0.965 |

(n=6)

Fig. 7: In vitro diffusion study tazarotene microsphere topical gel

Table 8: Photostability study of 0.1% tazarotene microsphere topical gel

| Description       | Initial drug content | Drug content after 8 h |
|-------------------|----------------------|------------------------|
| Test sample       | 87.27±2.32 %         | 80.63±1.42 %           |
| Control sample    | 87.27±2.32 %         | 87.26±0.89 %           |

CONCLUSION

The present study concluded successful preparation and optimization of 0.1% tazarotene-loaded microsphere gel with the enhanced availability of drug at the site of action. In vitro and Kinetic Modelling of Dissolution Data evaluation of microsphere gel revealed remarkable and enhanced topical retention of drug for prolonged period of time. A controlled release of tazarotene onto the skin over a prolonged period of time was beneficial for psoriasis treatment. This study provides future insights for developing controlled release microsphere gels for topical applications containing retinoid.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICT OF INTERESTS

Declared none

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