FORMULATION, OPTIMIZATION, AND CHARACTERIZATION OF TRANSDERMAL DRUG DELIVERY SYSTEMS CONTAINING EPLERENONE

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ABSTRACT

Objective: The proposed work was aimed at optimization, formulation, and characterization of transdermal patches of eplerenone for efficient transdermal delivery of the drug.

Methods: The log p estimation of eplerenone is 1.34, it was closer to standard worth. Log P value in a range of 1 to 4 indicates higher permeation through the skin. FTRIR study was carried out individually for drug, each polymer, and finished product (Patches) compared eplerenone and FTRIR spectra of pure drug and polymer. The calibration curve of eplerenone in Phosphate buffer pH 6.8 was analyzed.

Results: The selected range of eplerenone was found to be linear. A regression coefficient (R²) at 245 nm was found to be 0.994. Drug content outcomes additionally discovered uniform in all clusters in a range of 97 % to 98 %, that batches arranged with ERS 100 show great mechanical properties contrast with different polymers however helpless glue properties. The flatness of 4 cm² patches ranges from 348 ±0.087 mg to 387±0.527 mg. skin irritation it was produced irritation with negligible erythema following 10 d and unequivocal erythema, promptly obvious edema was produced following 12 d.

Conclusion: These after-effects of the in vivo skin irritation study recommended that advanced batch S9 doesn’t show any kind of significant disturbance on rodent skin for as long as 14 d and it was securely utilized around 24 h. the optimized batch S9 drug was constantly discharged through the Wistar rodent skin up to 16 hr and the delivery design was like an in vitro dissolution profile of the market product.

Keywords: TDDS, Eplerenone, ERS 100, In vivo skin irritation study

INTRODUCTION

Skin penetration energy is fundamental to the fruitful improvement of the transdermal restorative framework. Transdermal saturation of medication includes the following advances: Sorption by layer corneum, Infiltration of medication through the feasible epidermis, Uptake of medication by narrow organization in dermal papillary layer. Transdermal medication conveyance frameworks (TDDS) are measurements structures that include drug transport to feasible epidermal or potentially dermal tissues of the skin for neighborhood restorative impact while an exceptionally significant part of the medication is shipped into the foundational blood course. The glue of medicinal item to the skin and the proposed dose structure and course of the organization [9]. Despite the fact that the vast majority of the expository and recognizable proof boundaries was at that point performed by Chemo Pvt. Ltd. Mumbai (M. H.) India who give the identification test of eplerenone pure drug for research work [10].

Pre-formulation studies

Pre-formulation testing of the dynamic substances gives helpful data. It might be important to consider the physicochemical qualities of dynamic substance in the plan comparable to the proposed dose structure and course of the organization [9]. Despite the fact that the vast majority of the expository and recognizable proof boundaries was at that point performed by Chemo Pvt. Ltd. Mumbai (M. H.) India who give the identification test of eplerenone pure drug for research work [10].

MATERIALS AND METHODS

The pure drug eplerenone was purchased from Chemo Pvt. Ltd, Mumbai, Eudragit RS 100, Eudragit RL 100, Polyethylene glycol, PEG 400 were purchased from Chemdyes corporation, Rajkot, India, HPMC K15M from Loba Chemie Pvt. Ltd., Mumbai, India. Ethanol was obtained from Shree Chalhan Vihag Khandudyog Sahkari Mandli Ltd, Surat.

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Determination of λmax

For assurance of λmax stock solution of eplerenone (conc. 1000µg/ml) in methanol were readied [10]. 1 ml of the readied stock arrangement was additionally weakened to 100 ml. Coming about arrangements were examined in the range of 400 to 200 nm utilizing methanol as a clear with the assistance of a UV-visible spectrophotometer [11]. Normal triplicate readings were taken.

Calibration curve of eplerenone in pH-6.8 phosphate buffer

The above stock arrangement filtered for the most extreme absorbance utilizing UV max of eplerenone in phosphate buffer pH 6.8 was seen as 245 nm [11, 12]. The above stock arrangement (100 g/ml) was additionally weakened to get focus in the range of 10-50 g/ml. The absorbance of every arrangement was estimated utilizing a UV-Visible double beam spectrophotometer by putting reference standards of a particular medium. The standard bend produced for a whole range of conc. and the tests acted in triplicate.

The partition coefficient of the drug

Log P [13, 14], was estimated utilizing a separating funnel by shaking equivalent volumes of oil and watery stage.

Melting point identification

The Melting purpose of eplerenone was resolved to utilize the open capillary technique [15].

Permeation study of the pure drug

The in vitro drug discharge looks were finished by using Franz dispersion cell. The rodent skin of the stomach part was managed.

Original Article

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and hair was emptied and propped between the receptor and provider compartments. The receptor compartment was stacked up with 15 ml of scattering medium (Phosphate cushion pH 7.4) through examining port taking thought to oust all the air bubbles. The substances were blended at 500 rpm by distantly decided, Teflon covered minimal appealing touch to keep them all around mixed. Decisively measured 5 mg of eplerenone was separated in phosphate cushion pH 7.4 and set in receptor compartment [16]. At proper stretches of time, aliquots (3 ml) were assembled and sensible weaken the aliquot with phosphate cushion and absorbance was assessing at 245 nm using a twofold shaft UV spectrophotometer (Shimadzu SL-1800).

**Preliminary trial batches for selection of permeation enhancers**

The skin flux of eplerenone got without penetration enhancer was 75.25 µg/cm²/h and it was not adequate to gain focus on flux [17], for keeping up the helpful convergence of medication up to foreordained period.

**Table 2: Preliminary trial batches of polymers**

| Ingredient(s)(mg) | ERS1  | ERS2  | ERS3  | ERL1  | ERL2  | ERL3  | H1    | H2    | H3    |
|------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Eplerenone       | 49    | 49    | 49    | 49    | 49    | 49    | 49    | 49    | 49    |
| ERS100           | 100   | 200   | 300   | -     | -     | -     | -     | -     | -     |
| ERL100           | -     | -     | -     | 100   | 200   | 300   | -     | -     | -     |
| HPMC K15         | -     | -     | -     | -     | -     | 100   | 200   | 300   |       |

**Statistical optimization of the formulation variables using 3² full factorial experimental design**

Fundamental preliminary batches were arranged and assessed for the determination of different centralizations of polymers, plasticizers, and permeation enhancers. After-effects of fundamental preliminary clusters proposed that batches arranged with ERS and ERL 100 [20] show great mechanical properties however, helpless adhesive properties. 3² full factorial structures were select from Design Expert programming 9.0 for the advancement of conclusive detailing. This plan included three dependent variables (Y1, Y2, and Y3) or more referenced two independent variables (X1 and X2). The needly factors Y1 was rigidity (BS) of arranged patches, Y2 was drug release in the introductory first hour (Q1h) and Y3 was medicated discharge following 16 h (Q16h) [16, 19, 20].

**Method of preparation of transdermal patch of batches S1-S9 using 3² full factorial designs**

The transdermal patches containing eplerenone were readied utilizing various proportions of ERS100/ERL 100 and HPMC K15M. The polymer's focus was a change with this proportion of 250:50, 225:75, and 200:100 [16-18], by keeping the consistent load of polymer 300 mg with proportion (2:1) of ERS100/ERL 100: HPMC K15M, then permitted to grow for two hrs in water.

**Table 3: Formulation of eplerenone loading factorial design batches S1 to S9**

| Batch code | S1   | S2   | S3   | S4   | S5   | S6   | S7   | S8   | S9   |
|------------|------|------|------|------|------|------|------|------|------|
| Eplerenone (mg) | 49 | 49 | 49 | 49 | 49 | 49 | 49 | 49 | 49 |
| ERS/ERL 100 (mg) | 250 | 250 | 250 | 225 | 225 | 225 | 225 | 200 | 200 |
| HPMC K15 (mg) | 50 | 50 | 50 | 75 | 75 | 75 | 75 | 100 | 100 |
| Water (mL) | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 |
| Ethanol (mL) | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| PG (%) w/w | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| MO (%) w/w | 10 | 20 | 30 | 10 | 20 | 30 | 10 | 20 | 30 |

**Evaluation of TDDS**

**The thickness of the patch**

The thickness of the prescription stacked fix was assessed in different concentrations by using a micrometer screw measure and chooses the typical thickness and standard deviation for the equal to ensure the thickness of the prepared fix [10, 33].

**Drug content**

The measure of medication present in the fix was dictated by dissolving the fix in 100 ml of phosphate cradle pH 6.8. By then the plan is to be isolated through a channel medium and analyze the medicine using (UV technique) at 245 nm.

**Percentage moisture content**

The prepared patches were weighed exclusively and to be kept in a desiccators containing melded calcium chloride at room temperature for 24 h. After 24 h the movies are to be rechecked and decide the rate dampness content from the beneath referenced formula.

\[
\text{Percentage moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100
\]

**Percentage moisture uptake**

The gauged patches were kept in a desiccator at room temperature for 24 h containing a soaked arrangement of potassium chloride [34] to keep up 84% RH. After 24 h the movies are to be rechecked and decide the rate dampness take-up from the beneath referenced equation.

\[
\text{Percentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100
\]

**Weight uniformity**

The prepared patches were dried on the stove at 60° for 24 h prior to testing. A predetermined territory of fix is to be cut in various pieces of the fix and say something computerized balance [20, 34].
RESULTS AND DISCUSSION

The normal weight and standard deviation estemees are to be
determined from the individual loads.

Water vapor permeability

Glass vials of 5 ml limit were washed altogether and dried to a
consistent load on a stove. About 1 g of mekled Calcium chloride was
taken in the vials and the polymer films were fixed over the edge with the
assistance of a sticky tape. At that point, the vials were gauged and
put away in a mugginess chamber at 85 % RH condition [35] for a time
of 24 h. The vials were eliminated and weighed at different time
stretches like 3, 6, 12, 18, and 24 h to note down the weight pick up.

Folding endurance

A portion of the explicit territory was cut equitably and consistently
collapsed at a similar spot till it broke. The occasions the film could
be collapsed at a similar spot without breaking gave the estimation of the collapsing perseverance [36].

Percentage elongation break test

The rate stretching break was controlled by noticing the length not
long before the breakpoint, the rate extension can be resolved from the
beneath referenced formula.

\[
\text{Elongation percentage} = \frac{L_1 - L_2}{L_2} \times 100
\]

Where L1 is the final length of each strip and L2 is the initial length of each strip

Weight variation

The appraisal of weight variety was performed by weighing
independently drug stacked five patches of each plan on an
advanced equilibrium. The normal loads were determined and the
standard deviation from the normal loads was estimated.

Tensile strength

The tensile strength of the readied patches was measure by a
secretly gathered instrument. The elasticity of the fix was assessed
using a secretly assembled instrument. In which one side of fix fixed
into the iron screens and another side related with the paper holder
where the catch was inserted [37]. One string was joined with this
catch, which ignored the pulley and a little dish attached to the
furthest edge for holding the weight. Little pointer was annexed to
the string, which goes over the scale appended on the base plate. For
assessment of rigidity, the fix was pulled and stacks were step by
step added to the dish to assemble the pulling power till the fix was
broken. Full-scale loads needed to break the fix considered as a
force, putting the assessment of intensity into the condition
flexibility was measured.

Flatness

A transdermal patch should have a smooth surface and should not
strike with time. To survey this property evenness study was
performed [32]. In this, study one portion of the fix cut from the
center and two from each side. The length of each strip was assessed
and assortment long notes down. Zero percent narrowing will be
proportionate to 100 % levelness.

\[
\text{Percentage constriction} = \frac{L_1 - L_2}{L_2} \times 100
\]

pH

The patch was set in a beaker and was soaked with 10 ml of distilled
water and saved for 30 min. The pH was measure subsequent to
bringing the terminal of the pH meter in contact with the outside of
the plan and permit equilibrates for 2 to 3 min [34, 36].

In vitro drug release studies

The in vitro discharge study was finished with the semi-permeable
film using Franz dissemination cell [36]. The chamber contains two
chambers, the supplier and the receptor compartment. The supplier
compartment was open at the top and was introduced to the air. The
temperature was kept up at 37±0.5 °C and the receptor
compartment was outfitted with a testing port. The scattering
medium used was phosphate uphold (pH 7.4).

Ex-vivo diffusion study of final optimized matrix patch

For this examination recently yielded with ether Wistar rat skin was
gathered, first of hair from the skin was expelled then skin wash
with phosphate buffer solution lastly secured with aluminum foil
and put away at 3 to 5 °C in a cooler for permeation study [19, 37].

In vivo skin irritation study of transdermal patch

Skin irritation study intended to distinguish disturbance under
states of maximal pressure and during the appraisal of transdermal
drug products. A study was performed on 18 Wistar rats for 14 d.
Irritation study [17, 20, 38] performed on three groups (each group
has 6 rodents), to be specific Group 1 was doled out as a control
group with placebo patch, Group 2 apply with specific mentha oil
and put at 3 to 5 °C in a cooler for permeation study [19, 37].

Table 4: Solubility study of eplerenone

| Medium solubility | Solubility          | Calculated value |
|-------------------|---------------------|------------------|
| Ethanol           | Freely soluble       | 26 μg/ml         |
| Methanol          | Soluble             | 23.2 μg/ml       |
| Chloroform Soluble| Soluble             | 18.8 μg/ml       |
| Distilled Water   | Practically insoluble| 6 μg/ml          |
| pH 6.8 Buffer     | Soluble             | 19 μg/ml         |

The log p estimation of eplerenone 1.34, it was closer to standard worth. Log P value in a range of 1 to 4 indicates higher permeation through the skin.

Spectra of eplerenone in phosphate buffer pH 6.8

The standard stock solution was prepared as per the method described
in the methodology section and scanned by UV-spectrophotometer. The
UV absorption spectrum of eplerenone showed a peak at 245 nm against
blank and the same was used for further analysis.

Preliminary studies of pure drug permeation

The penetration flux of eplerenone across wistar rodents saw as
5.101 μg/cm2/h. The diffusion coefficient was 0.0116 x10^-8 cm2/h
and penetrability coefficient was 0.45 X 10^2/cm/h. The acquired
information of medication release study proposed that pure
medication having adequate permeation through the skin; however,
the got flux was insufficient to keep up consistent state plasma conc.
of medication all through the treatment [39]. Hence, further
improvement in flux accomplishes utilizing fundamental oils as
normal permeation enhancers. In this current exploration work
fundamental oil to be specific mentha oil (MO), was selected and
attempted [40-43].
Fig. 1: Spectra of eplerenone in phosphate buffer pH 6.8

Fig. 2: Calibration curve of eplerenone in phosphate buffer pH 6.8

Fig. 3: Comparative drug release profile of batches L1-L2

| S. No. | Concentration (μg/ml) | Absorbance |
|--------|-----------------------|------------|
| 1.     | 10                    | 0.330      |
| 2.     | 20                    | 0.514      |
| 3.     | 30                    | 0.751      |
| 4.     | 40                    | 1.001      |
| 5.     | 50                    | 1.283      |

Table 4: Data of concentrations and absorbance in phosphate buffer pH 6.8

Improvement in permeability using permeation enhancers

Gotten consequences of bunches PEC1 to PEC7 for development in penetration with various centralization of chose essential oils as enhancers uncovered that permeation increment with increment in the convergence of basic oils since they improve the diffusion of medication particles through the various layers of skin by parceling into the lipid cell of layer corneum. This was obvious from the after-effects of eplerenone permeation at 16 h from PEC2 to PEC7 with MO thus at various groupings of 10 % w/w and 20 % w/w of the all-out weight of dry polymer weight, results appeared in fig. 4. The higher diffusion was acquired by provided a rising request for basic oil.

Preliminary trial batches for the polymers

Preliminary trial batches ERS1 to H9 were prepared for the selection of patch forming polymer and its concentration.
Table 7: Physicochemical evaluation of eplerenone loading batches S1 to S9

| Batch code | Weight variation (mg) | Thickness (mm) | Drug content (%) | Flatness (%) | Folding endurance | % Moisture uptake | % Moisture loss |
|------------|----------------------|----------------|-----------------|-------------|------------------|------------------|----------------|
| S1         | 36±0.732             | 0.10±0.11      | 97.2±0.21       | 99.8±0.22   | 358±0.23         | 1.86±0.07        | 2.78±0.09      |
| S2         | 37±0.516             | 0.14±0.22      | 98.3±0.07       | 98.9±0.23   | 362±0.21         | 2.06±0.06        | 1.86±0.08      |
| S3         | 36±0.527             | 0.15±0.12      | 98.8±0.08       | 99.8±0.24   | 354±0.23         | 2.50±0.18        | 1.98±0.68      |
| S4         | 34±0.087             | 0.16±0.23      | 97.5±0.40       | 99.7±0.26   | 356±0.22         | 2.42±0.12        | 2.14±0.05      |
| S5         | 38±0.527             | 0.17±0.11      | 97.2±0.21       | 93.1±0.28   | 263±0.29         | 1.90±0.30        | 1.56±0.59      |
| S6         | 37±0.320             | 0.18±0.21      | 96.8±0.29       | 93.1±0.28   | 263±0.29         | 1.80±0.16        | 1.93±0.02      |
| S7         | 35±0.231             | 0.11±0.19      | 263±0.29        | 1.80±0.16   | 1.80±0.14        | 2.45±0.06        | 2.26±0.03      |
| S8         | 33±0.253             | 0.13±0.21      | 254±0.21        | 2.72±0.05   | 2.72±0.05        | 1.93±0.02        | 1.93±0.02      |

(Where n = 3, mean±SD)
Table 8: Results of dependent variables of batches S1 to S9

| Batch code | X1  | X2  | Y1             | Y2             | Y3             |
|------------|-----|-----|----------------|----------------|----------------|
| S1         |     |     | 10.42±0.23     | 72.18±0.22     | 3.51±0.01      |
| S2         | -1  | -1  | 11.36±0.40     | 74.56±0.21     | 3.62±0.02      |
| S3         | -1  | 0   | 12.62±0.32     | 76.21±0.65     | 3.65±0.02      |
| S4         | 0   | -1  | 13.51±0.12     | 79.02±0.50     | 3.70±0.03      |
| S5         | 0   | 0   | 14.26±0.28     | 81.03±0.45     | 3.75±0.03      |
| S6         | 0   | 1   | 15.53±0.20     | 83.12±0.06     | 3.81±0.02      |
| S7         | 1   | -1  | 16.45±0.63     | 85.63±0.41     | 3.85±0.01      |
| S8         | 1   | 0   | 17.76±0.03     | 88.01±0.72     | 3.92±0.04      |
| S9         | 1   | 1   | 18.22±0.04     | 90.22±0.52     | 4.98±0.03      |

(Where n = 3, mean±SD)

Analysis of variance and model equations for tensile strength of batches S1 to S9

For response surface analysis, a two-way analysis of variance was generated by Design Expert 9.0 software. The Model F-value was more than the tabulated F-value (3.44) which implies that the model is significant, and the higher value of R² (0.995) indicates good fitting of the model. The polynomial equation derived for the estimation was mention below.

Tensile strength±3.67+0.44* A+0.18 * B+0.075* AB+0.23* A^2-0.020*B^2 ---- [1]

Analysis of variance and model equations for drug released in Q1(h)

For response surface analysis, a two-way analysis of variance was generated by Design Expert 9.0 software. The Model F-value was more than the tabulated F-value (3.56) which implies that the model is significant and the higher value of R² (0.998) indicates good fitting of the model. The polynomial equation derived for the estimation was mention below [44, 45].

% CDR (16h) = 93.0956+3.63667 * A+1.55667 * B+-0.07 * AB+0.806667 * A^2+-1.08333 * B^2

Table 9: Kinetic models and regression coefficient

| S. No. | Equation           | Regression coefficient |
|--------|--------------------|------------------------|
| 1      | Zero-order         | 0.9916                 |
| 2      | First-order        | 0.5425                 |
| 3      | Higuchi            | 0.9752                 |
| 4      | Korsmeyer-Peppas   | 0.9514                 |
| 5      | Hixson Crowell     | 0.6803                 |
In vivo skin irritation study

The convention clarified in the system part utilized for skin irritation study. Saline solution delivering skin irritation responses contrasted and the disturbance happened after the utilization of Placebo fix as a group 2 and optimized batch (S9) as a group 3. Each group containing six rodents. Skin irritation was determined on the basis of standards 0 to 7 given in the system part and got.

Table 10: Skin irritation study of group–1 (Control group-0.9 % W/V saline)

| S. No. | Skin irritation symptom | D1 | D2 | D3 | D4 | D5 | D6 | D7 | D8 | D9 | D10 | D11 | D12 | D13 | D14 |
|--------|-------------------------|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|-----|
| 1      | 0                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 2      | 1                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 3      | 2                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 4      | 3                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 5      | 4                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 6      | 5                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 7      | 6                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 8      | 7                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |

P-Severity of skin injury

Table 11: Skin irritation study of group 2 (Applied with placebo patch)

| S. No. | Skin irritation symptom | D1 | D2 | D3 | D4 | D5 | D6 | D7 | D8 | D9 | D10 | D11 | D12 | D13 | D14 |
|--------|-------------------------|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|-----|
| 1      | 0                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 2      | 1                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 3      | 2                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 4      | 3                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 5      | 4                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 6      | 5                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 7      | 6                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 8      | 7                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |

Table 12: Skin irritation study of group 3 (Applied with drug batch–S9)

| S. No. | Skin irritation symptom | D1 | D2 | D3 | D4 | D5 | D6 | D7 | D8 | D9 | D10 | D11 | D12 | D13 | D14 |
|--------|-------------------------|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|-----|
| 1      | 0                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 2      | 1                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 3      | 2                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 4      | 3                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 5      | 4                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 6      | 5                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 7      | 6                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |
| 8      | 7                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -   | -   | -   | -   | -   |

Fig. 9: Before-skin irritation study and after-skin irritation study

Table 13: Stability studies results of optimized batch S9

| Stability conditions | Sampling time | Folding endurance | Drug content uniformity (%) | Ex-vivo drug release (%) |
|----------------------|---------------|-------------------|-----------------------------|--------------------------|
| Accelerated condition| Initial (0 d)  | 397±1.50          | 98.91±0.64                  | 94.39±0.15               |
| (40±2 °C)            | After 15 d    | 384±2.32          | 98.85±0.32                  | 94.31±0.64               |
| (And 75±5% RH)       | After 30 d    | 37±1.02           | 98.75±0.16                  | 94.17±0.10               |
| (Batch S9)           | After 180 d   | 36±2.04           | 98.42±0.06                  | 94.17±0.02               |
Comparisons with marketed preparation

Last optimized batch S9 contrasted and compared with marketed formulation, (Daksone) extended-release tablet for drug delivery study. The promoted item and enhanced cluster were exposed to in vitro disintegration concentrate for up to 16 h utilizing dissolution apparatus II. [51] Optimized transdermal patch exposed to in vitro concentrate with the assistance of glass slide on which wistar rodent skin connect and a patch was stick on the rodent skin [52]. The acquired medication release profile proposed that from the optimized batch S9 drug was constantly discharged through the Wistar rodent skin up to 16 hr and the delivery design was like the in vitro dissolution profile of the market product. This uncovered from the medication stacked transdermal patch constantly releases the drug in a controlled way up to 16 h.

Fig. 10: Comparative drug release of batch S9 and extended-release tablet

Table 14: Calculation of similarity factor for ER tablet (Daksone) and batch S9

| Time (h) | Rt % CDR ER tablet | Tt % CDR batch S9 | Rt-Tt | (Rt-Tt)^2 |
|----------|---------------------|-------------------|--------|-------------|
| 0.5      | 5.76                | 5.51              | 0.25   | 0.0625      |
| 1        | 12.80               | 11.98             | 0.82   | 0.6724      |
| 2        | 29.90               | 28.23             | 1.67   | 2.7889      |
| 3        | 47.62               | 46.15             | 1.47   | 2.1609      |
| 4        | 59.03               | 58.30             | 0.73   | 0.5329      |
| 8        | 70.21               | 69.52             | 0.69   | 0.4761      |
| 12       | 84.36               | 78.75             | 5.61   | 31.4721     |
| 16       | 93.44               | 89.02             | 4.42   | 19.5364     |
| Σ(Rt-Tt)^2 |                    |                   |        | (57.7022)    |

CONCLUSION

A regression coefficient (R²) at 245 nm was found to be 0.994. The Correlation Coefficient (R²) = 0.993 and Y = 0.022x+0.056 Regression coefficient (R2). This was obvious from the aftereffects of eplerenone permeation at 16 h from PEC2 to PEC7 with MO thus at various groupings of 10 % w/w and 20 % w/w of the all-out weight of polymer dry weight. Drug content outcomes were additionally discovered uniform in all clusters in a range of 97 % to 98 %. The ex-vivo release likewise proposed that the concentration of SO and PG both had a significant impact on drug release. The correlation coefficient (R²) of Higuchi’s model was seen as 0.9752, which shows the diffusion of medication from the readied patches. The determined estimation of eplerenone enhanced batch S9 was seen as 57.70.

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AUTHORS CONTRIBUTIONS

All the authors have equally contributed to this manuscript.

CONFLICT OF INTERESTS

The authors declare no conflict of interest, financial or otherwise.

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