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. FTIIR study was carried out individually for drug, each polymer, and finished product (Patches) compared eplerenone and FTIR 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 (R^2) 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 cm^2 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 medication is shipped into the foundational blood course. The glue of the transdermal medication conveyance framework [1-5], is basic to the security, viability, and nature of the item. Eplerenone, an aldosterone receptor foe like spironolactone, has been appeared to create supported expansions in plasma renin and serum aldosterone, steady with the hindrance of the negative administrative input of aldosterone on renin emission. The subsequent expanded plasma renin action and aldosterone circling levels don't beat the impacts of eplerenone [6-8]. The proposed work was meant to streamlining the plan and portrayal of transdermal patches of eplerenone for the productive transdermal conveyance of medication in drug framework to improve the antihypertensive impact of eplerenone. Sometimes *In vitro* transdermal permeation was carried using modified Keshary-Chein diffusion cells across rat epidermis [9].

MATERIALS AND METHODS

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

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].

Determination of λ_{max}

For assurance of λ_{max} 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

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 75.25µg/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.

Dose for the formulation of transdermal matrix patch of eplerenone

Diameter of Petri Plate =6.8 cm,

Area of Petri plate = $3.14 \times (3.4)^2 = 36.29$ cm²

Area of patch = 2 cm × 2 cm = 4 cm² the total No. of patches in each Petri-dish plate = Area of Petri plate/Area of patch =36.29/6 = 6.04 Now, one patch contains 8 mg of drug then 6.04 patches contain 48.33 mg of drug (49 mg).

Preliminary trial batches for selection of polymers

Primer preliminary trial batch ERS1 to H3, arranged by solvent evaporation method for choice of different fix framing polymers and their concentration. In which groups ERS1 to ERS3 were getting ready for the choice of Eudragit RS 100 (ERS 100) conc., ERL1 to ERL3 were set up for the determination of Eudragit RL 100 (ER) conc., H1 to H3 was set up for the choice of various evaluations and concentrations of HPMC K15M [17-19].

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

needy 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	200	200	200
HPMC K15 (mg)	50	50	50	75	75	75	100	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.

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

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.

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

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].

The normal weight and standard deviation esteems 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 1g of melded 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 24h 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.

$$\text{Elongation percentage} = \frac{L1 - L2}{L2} \times 100$$

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 stifle 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.

$$\text{Percentage constriction} = \frac{l1 - l2}{l1} * 100$$

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 apply with characteristic skin irritation, 0.9 % w/v saline; Group 2 apply with placebo patch, Group 3 apply with last optimized batch. Patch applied on the posterior of smooth skin of rodents for 23±1 h up to 14 d to a similar skin site.

RESULTS AND DISCUSSION

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	19µg/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 51.01 µg/cm2/h. The diffusion coefficient was 0.0116 x10-8 cm²/h and penetrability coefficient was 0.45×10^{-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].
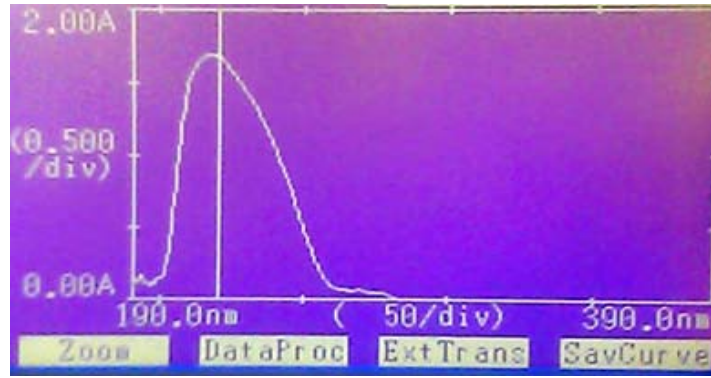
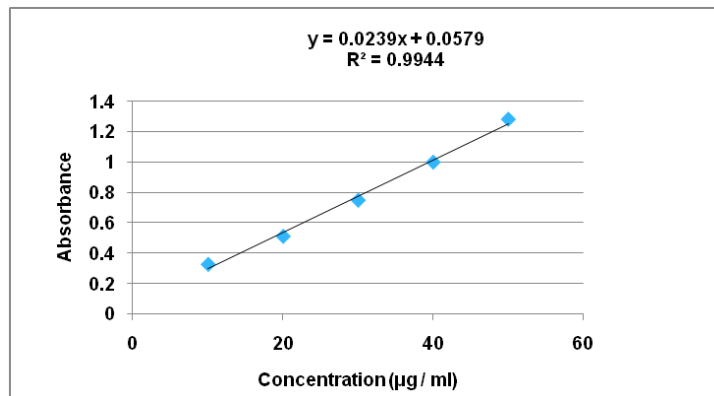**Fig. 1: Spectra of eplerenone in phosphate buffer pH 6.8**

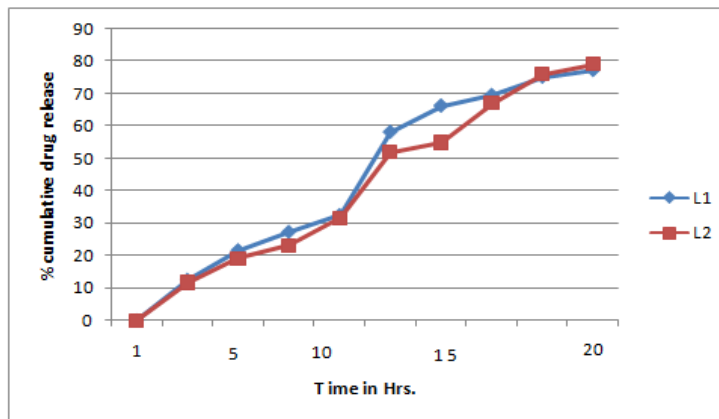**Fig. 2: Calibration curve of eplerenone in phosphate buffer pH 6.8**

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

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

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

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.
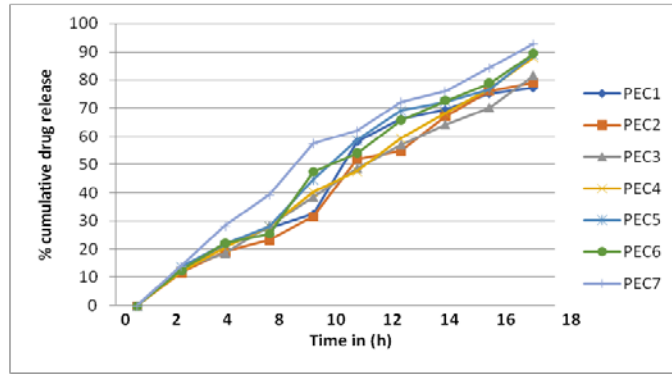
Fig. 4: Comparative drug release profile of batches PEC1 to PEC7

Table 5: Physicochemical parameters of batches ERS1 to ERL3

Batch code	Weight variation (mg)	Thickness (mm)	Drug content (%)	Flatness (%)	Folding endurance
ERS1	360±0.732	0.10±0.11	97.26±0.21	99.8±0.22	358±0.23
ERS2	373±0.516	0.14±0.22	98.34±0.87	98.9±0.23	362±0.21
ERS3	307±0.527	0.15±0.12	98.84±0.80	98.4±0.24	354±0.23
ERL1	346±0.087	0.16±0.23	97.52±0.40	99.7±0.26	356±0.22
ERL2	388±0.527	0.22±0.24	98.68±0.49	99.8±0.27	368±0.21
ERL3	378±0.320	0.18±0.21	97.79±0.52	98.1±0.17	346±0.20

(Where n = 3, mean±SD)

Table 6: Physicochemical parameters of batches H1 to H9

Batch code	Weight variation (mg)	Thickness (mm)	Drug content (%)	Flatness (%)	Folding endurance
H1	360±0.732	0.10±0.11	97.26±0.21	99.8±0.22	358±0.23
H2	373±0.516	0.14±0.22	98.34±0.87	98.9±0.23	362±0.21
H3	370±0.527	0.15±0.12	98.84±0.80	98.4±0.24	354±0.23
H4	346±0.087	0.16±0.23	97.52±0.40	99.7±0.26	356±0.22
H5	388±0.527	0.22±0.24	98.68±0.49	99.8±0.27	368±0.21
H6	378±0.320	0.18±0.21	97.79±0.52	98.1±0.17	346±0.20
H7	370±0.320	0.10±0.11	97.28±0.21	93.8±0.22	249±0.27
H8	353±0.231	0.11±0.19	96.84±0.29	93.1±0.28	263±0.29
H9	337±0.253	0.13±0.21	97.66±0.24	94.4±0.24	254±0.21

Table 7: Physicochemical evaluation of eplerenone loading batches S1 to S9

| Batch code	Weight variation (mg)	Thickness (mm)	Folding endurance	% moisture uptake	% Moisture loss
S1	360±0.732	0.10±0.11	358±0.23	1.86±0.07	2.78±0.09
S2	373±0.516	0.14±0.22	362±0.21	2.60±0.06	1.86±0.08
S3	369±0.527	0.15±0.12	354±0.23	2.50±0.18	1.98±0.68
S4	348±0.087	0.16±0.23	356±0.22	2.42±0.12	2.14±0.05
S5	387±0.527	0.19±0.24	368±0.21	1.90±0.30	1.56±0.59
S6	378±0.320	0.18±0.21	346±0.20	1.80±0.05	2.26±0.03
S7	370±0.320	0.10±0.11	249±0.27	1.63±0.21	2.45±0.06
S8	353±0.231	0.11±0.19	263±0.29	2.72±0.05	1.93±0.02
S9	337±0.253	0.13±0.21	254±0.21	1.98±0.16	1.80±0.14

(Where n = 3, mean±SD)
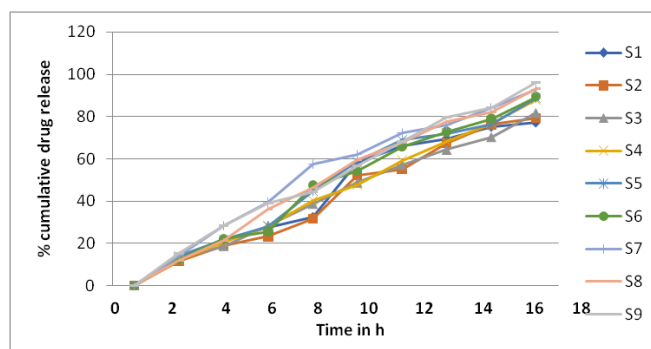
Fig. 6: Comparative drug release profile of batches S1-S9

Table 8: Results of dependent variables of batches S1 to S9

Batch code	Code value		Dependent variables		
S1	X1	X2	Y1	Y2	Y3
S2	-1	-1	10.42±0.23	72.18±0.22	3.51±0.01
S3	-1	0	11.36±0.40	74.56±0.21	3.62±0.02
S4	-1	1	12.62±0.32	76.21±0.65	3.65±0.02
S5	0	-1	13.51±0.12	79.02±0.50	3.70±0.03
S6	0	0	14.26±0.28	81.03±0.45	3.75±0.03
S7	0	1	15.53±0.20	83.12±0.06	3.81±0.02
S8	1	-1	16.45±0.63	85.63±0.41	3.85±0.01
S9	1	0	17.76±0.03	88.01±0.72	3.92±0.04
	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 R^2 (0.995) indicates good fitting of the model. The polynomial equation derived for the estimation was mention below.

$$\text{Tensile strength} + 3.67 + 0.44 * A + 0.18 * B + 0.075 * AB + 0.23 * A2 - 0.020 * B2 ----- [1]$$
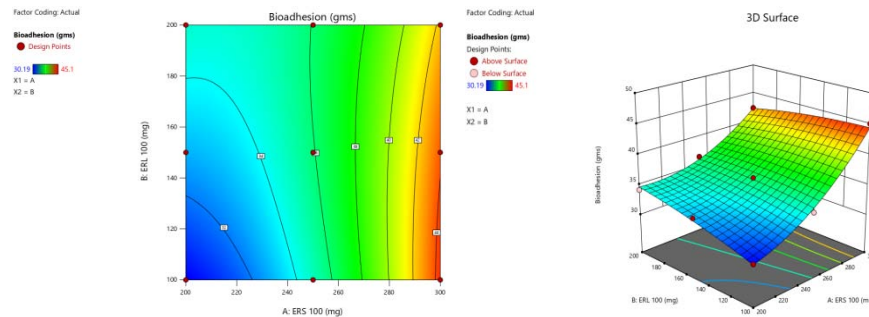

Fig. 7: Counter plot and (B) Response surface plot of the effect of polymer fixed weight ratio and mentha oil on tensile strength of batches s1 to s9

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 R^2 (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

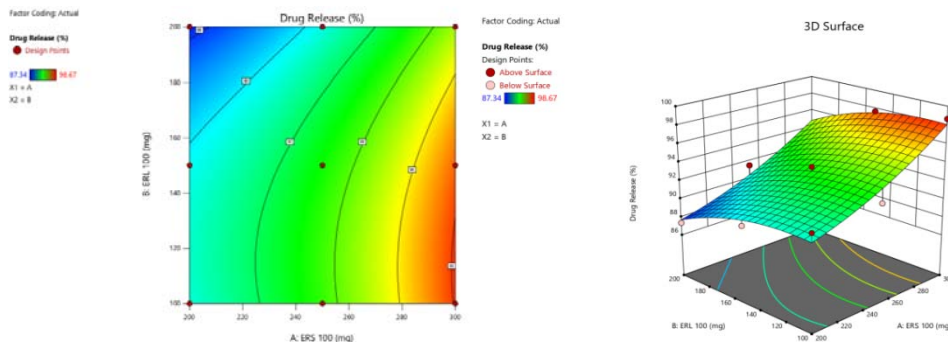Fig. 8: Counter plot and (B) Response surface plot show the effect of polymer fixed weight ratio and mentha oil on the percent drug released in 1 H from batches S1-S9

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 it. 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)

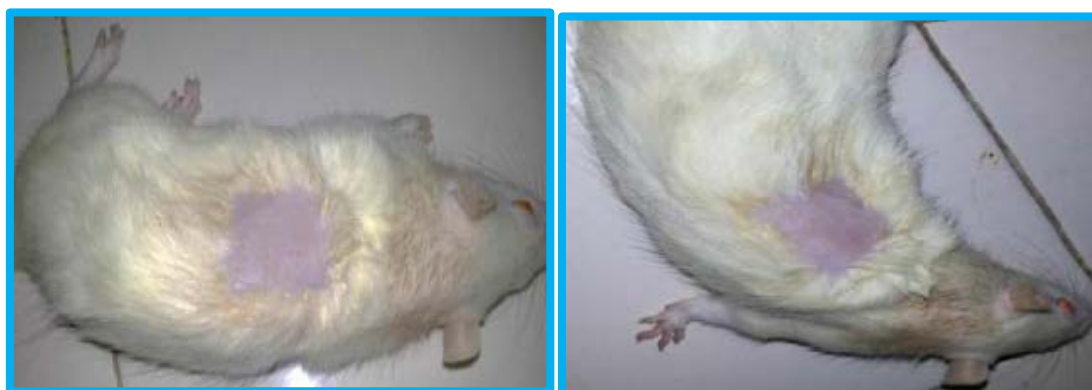| S. No.	Skin irritation symptom	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14
1	0	-	-	-	-	-	-	P	P	P	P	P	P	P	P
2	1	-	-	-	-	-	-	-	-	-	P	P	P	P	P
3	2	-	-	-	-	-	-	-	-	-	-	-	P	P	P
4	3	-	-	-	-	-	-	-	-	-	-	-	-	P	P
5	4	-	-	-	-	-	-	-	-	-	-	-	-	-	P
6	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-
7	6	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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	-	-	-	-	-	-	-	-	-	-	P	P	P	P
2	1	-	-	-	-	-	-	-	-	-	-	-	P	P	P
3	2	-	-	-	-	-	-	-	-	-	-	-	-	P	P
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	-	-	-	-	-	-	-	-	-	-	P	P	P	P
2	1	-	-	-	-	-	-	-	-	-	-	-	P	P	P
3	2	-	-	-	-	-	-	-	-	-	-	-	-	P	P
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	Initial (0 d)	397±1.50	98.91±0.64	94.39±0.15
condition	After 15 d	384±2.32	98.85±0.32	94.31±0.64
(40±2 °C	After 30 d	371±1.02	98.75±0.16	94.27±0.10
and 75±5% RH)	After 90 d	369±2.63	98.69±0.40	94.20±0.31
(Batch S9)	After 180 d	364±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.
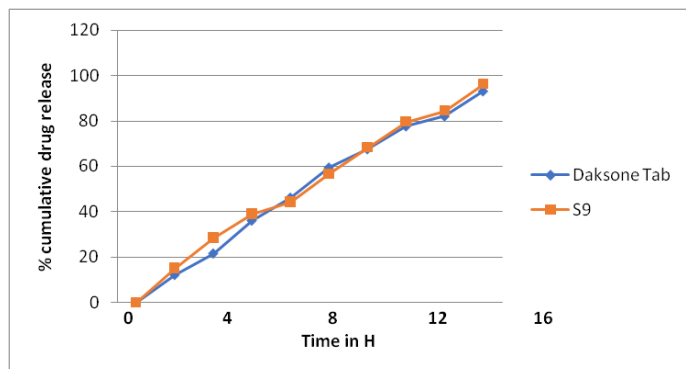

Fig. 10: Comparative drug release of batch S9 and extended-release tablet

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
				$\sum(Rt-Tt)^2$ (57.7022)

CONCLUSION

A regression coefficient (R^2) at 245 nm was found to be 0.994. The Correlation Coefficient (R^2) = 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 (R^2) 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.

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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