International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 15, Issue 1, 2023

Original Article

OPTIMIZATION, FORMULATION AND CHARACTERIZATION OF NANO BASED TDDS OF EPLERENONE

SHINDE RAMESH VITHOBA, MALARKODI VELRAJ*

Department of Pharmaceutical Sciences, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Chennai, Tamil Nadu, India, Chennai, Tamilnadu, India
***Email: malarkodisanna@gmail.com**

Received: 04 Jun 2022, Revised and Accepted: 15 Oct 2022

ABSTRACT

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

Methods: Eplerenone nanoparticles transdermal patches were formulated by the casting evaporation method. Transdermal patches were made using combinations of hydroxypropyl methylcellulose (HPMC), Eudragit RS 100. Physical characterization evaluation (organoleptic properties, pH, weight uniformity, thickness uniformity, percent moisture content, and tensile strength) was then performed. The permeation of eplerenone nanoparticles into the skin was evaluated using Franz diffusion cell.

Results: Eplerenone nanoparticles transdermal patches could be formulated by the casting evaporation method with the thickness of the patches ranged from 0.10±0.11 mm to 0.15±0.54 mm. The average weight of the patches 4 cm^2 patches ranged from 350±0.202 mg to 386±0.527 mg, and the percent moisture content ranged from 1.0 to 6.0%**.** Folding endurance of prepared patches was in the range of 355±0.20 to 368±0.20. Prepared batches NS1 to NS9 evaluated for percentage moisture uptake and loss as well as for pH measurement. The result of *in vitro* drug release study for batch NS9 containing 30 %/cm 2/h and 87.74 % released in 16 h.

Conclusion: All patches met the requirement of the physical characterization for the transdermal patch.

Keywords: TDDS, Eplerenone nanoparticle, ERS 100, Transdermal matrix

DOI: https://dx.doi.org/10.22159/ijap.2023v15i1.45433. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

The skin is one of the most extensive organs of the human body. This multi-layered organ receives approximately one-third of all blood circulating through body. With a thickness of about a millimetre, the skin separates the underlying blood circulation network from the outside environment. Skin permeation kinetics is vital to the successful development of transdermal therapeutic system. Transdermal drug delivery systems (TDDS) are dosage forms involve drug transport to viable epidermal and or dermal tissues of the skin for local therapeutic effect while a very major fraction of the drug is transported into the systemic blood circulation [1]. Eplerenone, an aldosterone receptor antagonist similar to spironolactone, has been shown to produce sustained increases in plasma renin and serum aldosterone, consistent with inhibition of the negative regulatory feedback of aldosterone on renin secretion. The resulting increased plasma renin activity and aldosterone circulating levels does not overcome the effects of eplerenone [2].

The use of nano-formulations has emerged as a potential suggests keeping away from barriers related with transdermal therapy [3]. Due to the merits of small particle size, higher drug retention, alongside with their targeting ability, nano-formulations have been regarded best TDDSs. Accordingly, many strategies have been adopted to enhance the transdermal delivery of bioactive agents using nanoparticulate drug delivery systems, such as lipo-some, transferosomes, ethosomes, dendrimers and microemulsions. Liposomes as one of the transdermal delivery systems, have been studied due to the fact that the 1980s and have attracted a lot of interest. Nevertheless, liposomes do no longer penetrate deeply into the skin of rats and are restrained to the higher layer of the skin. By contrast, transferosomes, ultra-flexible liposomes, signify a promising lipid-based vesicular system that is significantly exploited in the area of transdermal drug delivery. As an end result of their ultra-flexible membrane characters, they have the potential to deliver the drug both into or via the skin, relying on the application, with excessive efficacy. The vesicular transferosomes are greater elastic than different vesicular delivery systems, such as liposomes, and are accordingly properly appropriate for skin penetration [4, 5]. The proposed work was aimed to optimization the formulation and characterization of transdermal patches of eplerenone for efficient transdermal delivery of the drug in the pharmaceutical system to enhance the antihypertensive effect of eplerenone.

MATERIALS AND METHODS

Materials

Eplerenone were taken from the Chemo Pvt Ltd, Mumbai, Eplerenone nanoparticles were formulated from hydroxypropyl methylcellulose (HPMC), Eudragit RS 100, Other materials included HPMC (LOBA Chemie Pvt. Ltd., Mumbai, India), Eudragit RS 100 (Chemdyes corporation, Rajkot, India), Eudragit RL 100 (Chemdyes corporation, Rajkot, India), Propylene glycol (Chemdyes corporation, Rajkot, India), PEG 400 (Chemdyes corporation, Rajkot, India), ethanol (Shree chalthan vibhag khand udyog sahkari mandli Ltd, Surat).

Top-down syntheses

In this strategy, destructive methodology is utilized. Beginning from bigger particle, which deteriorated into littler units and afterward, these units are changed over into reasonable NPs. Instances of this technique are crushing/grinding. The processing technique was utilized for this reason and the drug powders were finely processed for various time frames with the assistance of artistic balls and a notable planetary plant [6]. They demonstrated the impact of processing time on the general size of the NPs through various portrayal strategies and characterized their surface morphology and size by the SEM, TEM and zeta potential [7].

Differential scanning calorimetry

The DSC of the eplerenone nanoparticle was recorded by a differential scanning calorimeter equipped with a computerized data station. The DSC measurements were performed on a DSC 60,

Shimadzu, Japan instrument. Accurately weighed sample were placed in sealed aluminium pans before heating under nitrogen flow (20 ml/min) at a scanning rate of 100c/min [8]. An empty aluminium pan was used as a reference. Melting point was determined for the identification of drug nanoparticle [9].

Scanning electron microscopy

Scanning electron microscopy of drug nanoparticles was carried to determine the external morphology. The sample was mounted directly onto the SEM sample holder using double-sided sticking tape and images were recorded at the required magnification at an acceleration voltage of 20 kV using a scanning electron microscope [10, 11].

Dose for the formulation of transdermal matrix patch of eplerenone

Diameter of Petri plate =6.8 cm,

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

Area of patch = $2\ cm \times 2\ cm = 4\ cm^2$

Total no. of patches in each Petri plate = Area of Petri plate/Area of patch=36.29/6= 6.04

Now, one patch contains 8 mg of the drug, then 6.04 patches contain 48.33 mg of the drug (49 mg).

Table 1: Formulation of nano-size eplerenone loading factorial design batches NS1 to NS9

Batch code	NS1	NS2	NS3	NS4	NS5	NS6	NS7	NS8	NS9
Eplerenone (mg)	49	49	49	49	49	49	49	49	49
ERS 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 of dry polymer Wt.	20	20	20	20	20	20	20	20	20
MO (%)w/w of dry polymer wt.	10	20	30	10	20	30	10	20	30

Evaluation of Tdds

Thickness of the patch

The thickness of the medication stacked fix was estimated in various focuses by utilizing an micrometre screw gauge and decides the normal thickness and standard deviation for the equivalent to guarantee the thickness of the readied patch [12, 13].

Drug content

The amount of drug present in the patch was determined by dissolving the patch in 100 ml of phosphate buffer pH 6.8. At that point, the arrangement is to be separated through a channel medium and dissect the medication utilizing (UV method) at 245 nm [14, 15].

Percentage moisture content

The prepared patches were weighed exclusively and to be kept in a desiccator containing melded calcium chloride at room temperature for 24 h. After 24h the movies are to be rechecked and decide the rate dampness content from the beneath referenced formula [16].

$$\%\ \text{moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100 \ldots\ldots (1)$$

Percentage moisture uptake

The weighted patches were kept in a desiccator at room temperature for 24 h containing a saturated solution of potassium chloride in order to maintain 84% RH. After 24 h the films are to be reweighed and determine the percentage moisture uptake from the below-mentioned formula [17].

$$\%\ \text{moisture content} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100 \ldots\ldots (2)$$

Water vapor permeability

Glass vials of 5 ml capacity were washed thoroughly and dried to a constant weight in an oven. About 1g of fused Calcium chloride was taken in the vials and the polymer films were fixed over the brim with the help of an adhesive tape [18]. Then the vials were weighed and stored in a humidity chamber at 85 % RH condition for a period of 24 h. The vials were removed and weighed at various time intervals like 3, 6, 12, 18 and 24 h to note down the weight gain [19, 20].

Weight uniformity

The prepared patches were dried in an oven at 60° for 24 h before testing. A specified area of the patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights [21].

Folding endurance

A strip of the specific area was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance [22].

Percentage elongation break test

The percentage elongation break was determined by noting the length just before the breakpoint; the percentage elongation can be determined from the below-mentioned formula [23].

$$\text{Elongation percentage} = \frac{L1 - L2}{L2} \times 100 \ldots\ldots (3)$$

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

Weight variation

The assessment of weight variation was performed by weighing individually drug-loaded five patches of every formulation on a digital balance. The average weights were calculated and the standard deviation from the average weights measured [24].

Tensile strength

Tensile strength of the prepared patches was measured by a privately collected instrument. The tensile strength of the patch was estimated utilizing a privately gathered instrument. In which one side of patch fixed into the iron screens and another side was associated with the paper holder where snare was embedded. One string was attached with this snare, which disregarded the pulley and a little dish appended to the opposite end for holding the weight. Little pointer was appended to the string, which goes over the scale attached on the base plate [25]. For estimation of tensile strength, patch was pulled and loads were bit by bit added to the dish to build the pulling power till the patch was broken. All out loads required to break the patch are considered as power, placing the estimation of power into the equation elasticity was measured. Tensile strength= × (+/). Where F is the power required to break; a, b, and L are the width, thickness and length of the patch individually and l is an extension of patch at the breakpoint [26].

Flatness

A transdermal patch ought to have a smooth surface and ought not choke with time. To assess this property flatness study was perform. In this study one segment of patch cut from the middle and two from each side. The length of each strip was estimated and a variety long note down. Zero percent narrowing will be proportionate to 100 percent flatness [27].

$$\text{Percentage constriction} = \frac{l1-l2}{l1} \times 100 \ldots\ldots (4)$$

pH

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 [28].

***In vitro* drug release studies**

The *in vitro* release study was done with the semi-porous film utilizing Franz diffusion cell. The chamber comprises of two chambers, the giver and the receptor compartment. The giver compartment was open at the top and was presented to air [22]. The temperature was kept up at 37±0.5 ° C and the receptor compartment was furnished with testing port. The dispersion medium utilized was phosphate support (pH 7.4) [21].

RESULTS AND DISCUSSION

Table 2: Solubility study of eplerenone

Medium solubility	Solubility	Calculated value
Ethanol	Freely soluble	29 µg/ml
Methanol	Soluble	24 µg/ml
Chloroform Soluble	Soluble	19 µg/ml
Distilled Water	Practically insoluble	7 µg/ml
pH 6.8 Buffer	Soluble	21 µg/ml

Solubility for eplerenone Nanoparticle proposed that uninhibitedly dissolvable in organic solvents, dissolvable in phosphate support pH 6.8 and for all intents and purposes insoluble in distilled water. In any case, a transdermal patch apply on the skin, in this manner to assess permeation of medication through skin pH, phosphate buffer pH 6.8 was select as a dispersion mode for additional investigation.

Table 3: The DSC test on eplerenone was presented below

S. No.	Stage	Temperature
1	Onset	198.22 °c
2	Peak	198.25 °c
3	End set	199.65 °c

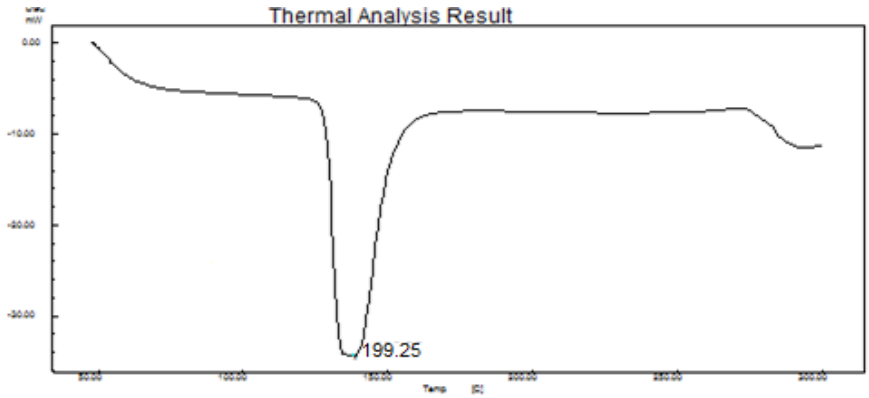

Fig. 1: Thermal analysis result of eplerenone nanoparticle

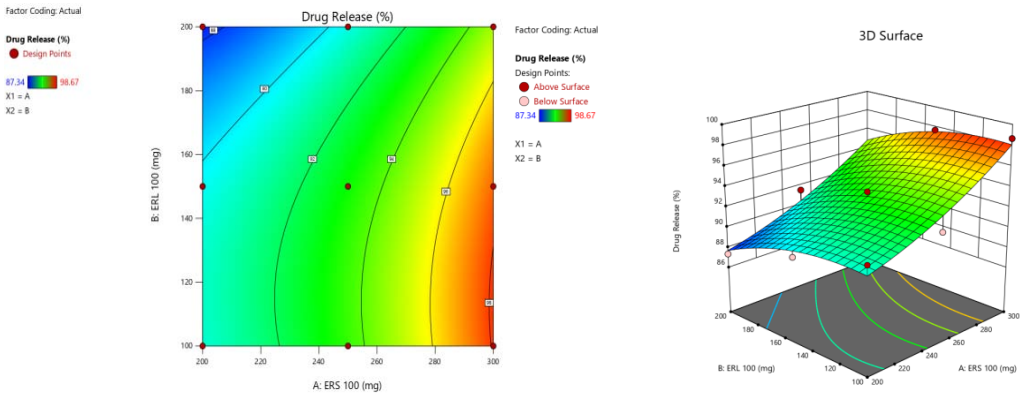

Fig. 2: Counter plot and (B) Response surface plot show the effect of polymer fixed weight ratio and mentha oil on the percent drug released in 1h from Batches NS1-NS9

Due to drug entrapment in the lipid, the melting point of eplerenone (pure drug) was 199.25 °C (fig. 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 R^2 (0.998) indicates good fitting of model. The polynomial equation derived for the estimation was mention below [15].

% CDR (16h) = 93.0956+3.63667* A+-1.55667* B+-0.07* AB+0.806667* A^2+-1.08333* B^2. .... Eq. (5)

3^2 Factorial Design in Design expert programme with Polynomial Quadratic Model and Multiple Linear Regression approach was used to optimize formulation and process parameters for nano-based transdermal patches formulation. The quadratic model suggests a P value of 0.0001 in the sum of squares. Selected the highest-order polynomial with significant additional terms and no aliasing. The chosen model has a minor lack of fit, as evidenced by the P-value of 0.0001 obtained from the Lack of Fit test. The Model F-value of 3.56 indicates that the model is statistically significant. An F-value of this magnitude has a 0.01 % chance of occurring due to noise. Model terms with P-values less than 0.05 are significant. The Adjusted R^2 of 0.998 is reasonably close to the Predicted R^2 of 0.9897; that is, the difference is less than 0.2. When all other factors are maintained constant, the coefficient estimate provides the expected change in response per unit change in factor value. In an orthogonal design, the intercept is the overall average response of all the runs. The coefficients are modifications based on the factor settings around that average.

The high levels of the factors are coded as+1 and the low levels of the factors are coded as-1 by default. By comparing the factor coefficients, the coded equation can be used to determine the relative impact of the components. It was discovered from the data that there was a good association between drug release (R^2 = 0.9841), It determines whether there is an increase in polymer concentration (when using ANOVA) It exhibits P<0.0001. It could be because of the influence of lower concentration and higher plasticizer concentrations. P-value = 0.0001 was calculated using ANOVA.

Scanning electron micrographs (SEM)

The surface morphology of nanoparticles is another important parameter which influences the drug release and drug absorbance properties. The evaluation of the surface morphology of the prepared formulations was done by the help of SEM analysis. Examination of SEM images of the prepared nanoparticles revealed that these were spherical. SEM images of formulation were presented in fig. 3. The spherical shape of these nanoparticles is confirmed by the SEM analysis.

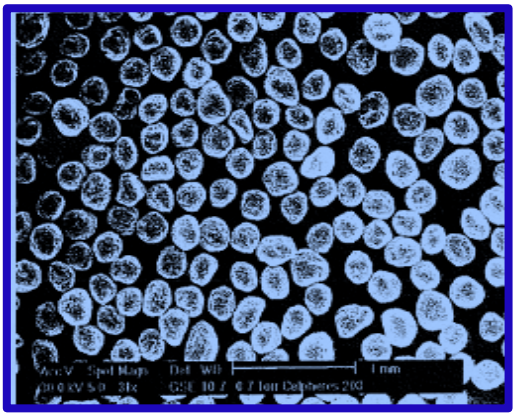

Fig. 3: Scanning electron micrographs of eplerenone nanoparticle

Aspect ratio

Aspect ratio was done for the nanoparticle sphericity for the flow property. Hot stage microscope was used for the measurement of the height and width of the nanoparticle. Aspect ratio was calculated from the following formula: From the above result aspect ratio of the nanoparticle was found to be 1.039. Guyot M. *et al.* has reported aspect ratio of the nanoparticle-based patches [14].

$$\text{Aspect ratio} = \frac{\text{Length of nanoparticle}}{\text{Width of nanoparticle}} \ldots\ldots\ldots\ldots (6)$$

Aspect ratio should be very near to 1 for the best spherical shape.

Partition coefficient

The log p estimation of eplerenone nanoparticle was 1.70, it was closer to standard worth. Log P value in a range of 1 to 4 indicates higher permeation through the skin.

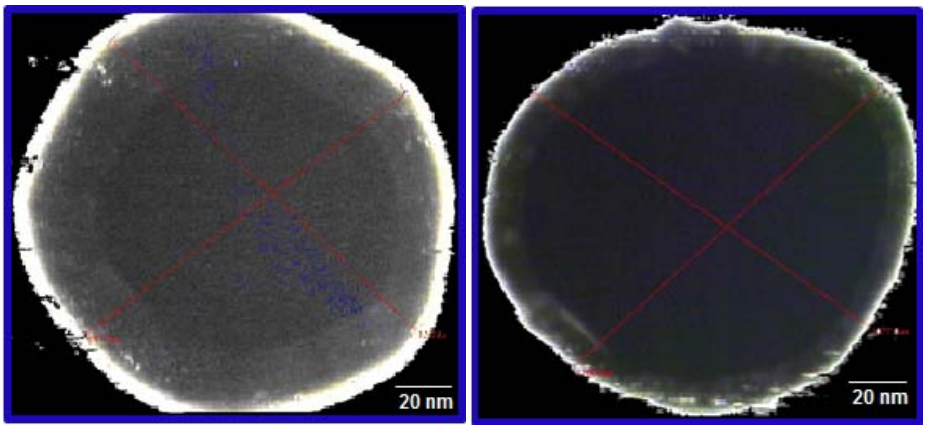

Fig. 4: Aspect ratio of eplerenone nanoparticle

Transdermal patch for eplerenone was effectively arranged utilizing HPMC K15M and ERS 100 as a patch shaping polymers by dissolvable dissipation technique and last medication stacked patch was discover by formulation of examinations from the Arranged batch NS1 to NS9 were assess for various physiochemical parameter. After-effects of the physicochemical parameter of batches S1 to S9 speak to in table 7.2.6. Drug-loaded films (4 cm2) were weighing using Digital electronic balance Shimadzu, Japan. The

weight of 4 cm2 patches ranged from 350±0.202 mg to 386±0.527 mg. In all the cases, the determined standard deviation esteems were low, which shows that the readied patches were uniform in weight, and along these lines, all the bunches passed the weight variety according to limits given in legitimate books. Acquired outcomes proposed that medication was consistently scattered in to polymeric scattering. With the assistance of a micrometer check, the thickness of fix was measure at six positions and the normal was note down. Prajapati ST *et al.* reported that the standard limits for the physicochemical evolution of the transdermal patches. [2] The result of batches NS1 to NS9 revealed that there were minor differences between the thicknesses of all the formulations; it was obtained in between 0.10±0.11 mm to 0.15±0.54 mm. Batch NS6 shows the highest thickness and NS4 shows the lowest thickness, this happens due to the different in polymer concentration and distribution difference over the Petri plate. Drug content of the transdermal patch was performed to find out the loading of the drug is uniform in the formulation or not. Folding endurance of prepared patches was in range of 355±0.20 to 368±0.20. Depending upon the concentration of propylene glycol and mentha oil, the results of folding endurance might be differed. Batches NS1 shows highest folding endurance with 368±0.20 indicates that the patches had sufficient mechanical strength and it would be remained as such during the treatment on the application site. The smoothness was measure manually for the prepared transdermal patch. An obtained result of the flatness study suggested that the length of the patch strip, before and after cuts was remain the same and it shows 2 to 3% constriction in all nine batches. Prepared batches NS1 to NS9 evaluated for percentage moisture uptake and loss as well as for pH measurement.

Table 4: Physicochemical evaluation of Eplerenone nanoparticle loading batches NS1-NS9

Batch code	Weight variation (mg)	Thickness (mm)	Folding endurance	% Moisture uptake	% Moisture loss
NS1	369±0.527	0.12±0.04	368±0.20	1.63±0.04	1.56±0.59
NS2	378±0.320	0.13±0.23	263±0.29	1.90±0.25	1.80±0.15
NS3	369±0.527	0.12±0.12	356±0.23	2.40±0.18	1.96±0.68
NS4	370±0.320	0.10±0.54	356±0.22	2.32±0.18	2.13±0.05
NS5	386±0.527	0.14±0.24	364±0.24	1.93±0.35	1.46±0.09
NS6	373±0.320	0.15±0.54	356±0.28	1.78±0.05	2.27±0.05
NS7	373±0.324	0.13±0.11	355±0.20	1.63±0.01	2.55±0.32
NS8	350±0.202	0.12±0.54	360±0.20	2.70±0.05	1.25±0.02
NS9	351±0.301	0.10±0.74	355±0.62	1.56±0.64	1.84±0.69

(Where n = 3, mean±SD)

***Ex-vivo* skin permeation study of eplerenone nanoparticle**

Plot of a combined measure of drug release versus time create for permeation contemplates and speak to in fig. 6. From this plot, permeation kinetic analysis, for example, penetration flux, permiability coefficient and enhancement proportion were determined. The outcomes uncovered that batch NS9 containing 30 %/cm2/hr and 87.74 % released in 16 h. Medication permeation improve with the higher grouping of SO because of the nearness of unsaturated fats, which change the structure of layer corneum and increment the dispersion of medication atoms through the various layers of the skin. Mittal A *et al.* reported that the diffusion coefficient of drugs in a PSA matrix is affected by the type of functional group of the drug. [15] The aftereffects of ex-vivo discharge likewise proposed that the concentration of SO and PG both had a significant impact on medicate discharge since unsaturated fats of SO improves the lipid dissolvability and PG improves water solvency by changing the extremity of fluid layer and improve solubilizing capacity for lipid particles. In this manner, consolidation of PG as a plasticizer in the medication stacked transdermal patches might be helpful for improving the physical quality just as drug release properties, thus use for achieving required medication permeability through the skin. The pace of medication release additionally relies upon choice of polymer and its conc. Medication release increments with increment in the convergence of the two polymers HPMC K15M and ERS 100 in light of the fact that hydrophilic nature of HPMC K15M and ERS 100 improve hydration and expanding property, which at last prompts swelling release in the introductory first hour. The arrival of medication from the polymeric framework happens as water enters inside the network, which makes the polymers swell, bringing about the controlled arrival of medication for a foreordained period. Anilreddy *et al.* showed an effect of the polymer concentration on the realease of the drug [7].

Table 5: Permeation kinetic parameters of batches NS1 to NS9

Batch code	Transdermal flux Jss 2/h)	Lag time (h)	Permeability coefficient (Kp) (cm/h)	Diffusion coefficient (D) (cm/h×10^{-8})	Enhancement ratio
NS1	97.6±0.34	1.26±0.2	1.24×10^{-3}±0.04	0.01236±0.05	1.234±0.01
NS2	98.6±0.15	1.33±0.4	1.30×10^{-3}±0.10	0.01390±0.18	1.235±0.02
NS3	119.0±0.11	1.34±0.6	1.45×10^{-3}±0.74	0.01472±0.17	1.337±0.03
NS4	121.3±0.21	1.26±0.7	1.50×10^{-3}±0.56	0.0158±0.14	1.339±0.04
NS5	129.0±0.10	1.34±0.2	1.58×10^{-3}±0.65	0.0159±0.14	1.436±0.03
NS6	131.2±0.41	1.32±0.2	1.61×10^{-3}±0.58	0.023±0.16	1.448±0.04
NS7	137.6±0.20	1.37±0.1	1.72×10^{-3}±0.65	0.025±0.10	1.548±0.06
NS8	152.1±0.02	1.32±0.4	1.79×10^{-3}±0.15	0.029±0.10	1.623±0.08
NS9	164.4±0.04	1.33±0.4	1.90×10^{-3}±0.16	0.0352±0.06	1.687±0.09

(Where n = 3, mean±SD)

Table 6: 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

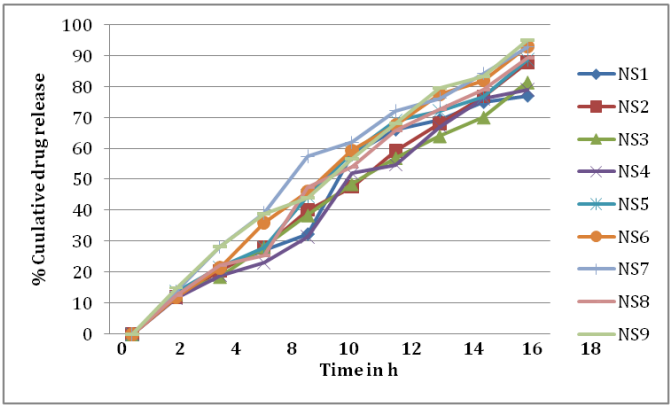

Fig. 6: Comparative drug release profile of batches NS1-NS9

In ex-vivo drug delivery information of last chose optimized batch was exposed to various kinetic models to contemplate the instrument of medication discharge from the patch and through the skin. Gannu R. *et al.* reported a regression analysis of the nanoparticle based patch [27] Regression coefficient additionally recommended that medication discharge from the patch follow zero request and from the patch tranquilize was discharge ceaselessly in a controlled way up to 16 h. The correlation coefficient (R^2) of Higuchi's model was seen as 0.9772 that shows diffusion of medication from the readied patches. In this manner, the chose batch NS9 followed zero order. Medication release component happen first by growing of polymer and drug was diffuse out from the matrix, so it follows Higuchi's and Korsmeyer-Peppas model more effectively.

Stability study

The optimized batch NS9 exposed for stability studies as per ICH guidelines for 6 mo. The samples assessed for the drug content, folding endurance and ex vivo permeation study. The after-effect of this examination shows that the items have awesome steadiness at room temperature. Sharma S. *et al.* show effect of stability study on formulations [26] Consequences of ex vivo diffusion study, drug content and folding endurance likewise proposed that expansion in temperature measure of dampness in patch diminished because of this patch become brittle. Consequences of an improved batch uncovered that final formulation was steady at accelerated condition at 40±2 °C and 75±5 % RH. It uncovered that, readied patches stable and keeps up its physical respectability all through the investigation.

Table 7: Stability studies results of optimized batch NS9

Stability conditions	Sampling time	Folding endurance	Drug content uniformity (%)	Ex-vivo drug release (%)
Accelerated condition	Initial (0 d)	397±1.50	98.70±0.02	95.30±0.03
(40±2oC and 75±5%	After 15 d	384±2.32	98.54±0.13	95.21±0.08
RH)	After 30 d	371±1.02	98.21±0.10	94.19±0.15
(Batch NS9)	After 90 d	369±2.63	98.14±0.23	94.18±0.23
	After 180 d	364±2.04	98.02±0.51	94.07±0.14

(Where n = 3, mean±SD).

CONCLUSION

Eplerenone nanoparticles have been successfully formulated into transdermal patches using combinations of hydroxypropyl methylcellulose (HPMC), Eudragit RS 100 Physical characterization of Eplerenone nanoparticles transdermal patches showed the uniformity of Eplerenone nanoparticle transdermal patches. Eplerenone can be released from the transdermal patch and can be predicted that all eplerenone will be released in 16 h. eplerenone can penetrate into the skin and formulating eplerenone nanoparticles. Overall findings from this research show that the limitation of oral eplerenone administration can be solved by formulating eplerenone into eplerenone nanoparticles transdermal patches, especially for Antihypertensive therapy.

ACKNOWLEDGEMENT

The authors are grateful to VISTAS, Chennai, and Hon. Shri. Babanrao Pachpute Vichardhara Trust's, Parikrama Group of Institutions, Kashti, for providing the required facilities for doing this work.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have equally contributed in this manuscript.

CONFLICT OF INTERESTS

No potential conflict of interest was declared by the authors.

REFERENCES

1. Oza NA, Sahu AR, Patel DM, Patel PU, Patel LD, Koshia HG. Transdermal patch of carvedilol by 32 full factorial design studies on optimization of reservoir-type transdermal patch using carvedilol using 3 2 full factorial design. Int J Res Med. 2013;2(4).
2. Prajapati ST, Patel CG, Patel CN. Formulation and evaluation of transdermal patch of repaglinide. ISRN Pharm. 2011;2011:651909. doi: 10.5402/2011/651909. PMID 22389856.
3. Patel RP, Professor A, Patel G, Patel H, Baria K, Patel AS. Dosage forms and tech. Res J Pharm Dosage Forms Technol. 2009. p. 1.
4. McDaid DM, Deasy PB. Formulation development of a transdermal drug delivery system for amlodipine base. International Journal of Pharmaceutics. 1996 May 14;133(1-2):71-83. doi: 10.1016/0378-5173(95)04412-4.
5. Nayak B, Pattanayak D, Ellaiah P, Das S. Formulation design preparation and *in vitro* characterization of nebivolol transdermal patches. Asian J Pharm. 2011 Jul;5(3):175-82. doi: 10.4103/0973-8398.91994.
6. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol. 2008;26(11):1261-8. doi: 10.1038/nbt.1504.

7. Anilreddy DRB. *In vitro* characterzatioan and evaluation of transdermal drug delivery system for metoprolol tartarate. Asian Journal of Pharmaceutical Research and Health Care. 2010;2(4):325-9.
8. Mishra AD, Khunt DM, Ghayal AH, Patel CN, Shah DR. Formulation and optimization of ethosomes for transdermal delivery of felodipine. Res J Pharm Technol. 2012;5(12).
9. Abdallah MH, Abu Lila ASA, Shawky SM, Almansour K, Alshammari F, Khafagy ES. Experimental design and optimization of nano-transfersomal gel to enhance the hypoglycemic activity of silymarin. Polymers (Basel). 2022 Feb 1;14(3). doi: 10.3390/polym14030508, PMID 35160498.
10. Mishra AD, Patel CN, Shah DR. Formulation and optimization of ethosomes for transdermal delivery of ropinirole hydrochloride. Curr Drug Deliv. 2013 Dec 27;10(5):500-16. doi: 10.2174/1567201811310050002, PMID 23410071.
11. Rao MR, Sonavane V, Kulkarni S, Magar M, Zope A, Karanjkar P. Design of transdermal patch of ketoprofen by full factorial design for treatment of rheumatoid arthritis. J Drug Delivery Ther. 2019 Mar 15;9(2):197-205. doi: 10.22270/jddt.v9i2.2549.
12. Lankaranian D, Reis R, Henderer JD, Choe S, Moster MR. Comparison of single thickness and double thickness processed pericardium patch graft in glaucoma drainage device surgery: a single surgeon comparison of outcome. J Glaucoma. 2008 Jan;17(1):48-51. doi: 10.1097/IJG.0b013e318133fc49, PMID 18303385.
13. Jamakandi VG, Mulla JS, Vinay BL, Shivakumar H. Formulation, characterization, and evaluation of matrix-type transdermal patches of a model antihypertensive drug. Asian J Pharm. 2009;3(1). doi: 10.4103/0973-8398.49177.
14. Guyot M, Fawaz F. Design and *in vitro* evaluation of adhesive matrix for transdermal delivery of propranolol. Int J Pharm. 2000 Jun 20;204(1-2):171-82. doi: 10.1016/s0378-5173(00)00494-4, PMID 11012001.
15. Mittal A, Sara US, Ali A, Mohammed A. Design, development, physicochemical, *in vitro* and *in vivo* evaluation of monolithic matrix type transdermal patches containing nitrendipine. Pharm Dev Technol. 2009;14(4):422-34. doi: 10.1080/10837450902748388, PMID 19630699.
16. Shinde R, Velraj M. Formulation, optimization, and characterization of transdermal drug delivery systems containing eplerenone. Int J Appl Pharm. 2022 Jan 7;14(1):198-207. doi: 10.22159/ijap.2022v14i1.42827.
17. Hardainiyan S, Kumar K, Nandy BC, Saxena R. Design, formulation and *in vitro* drug release from transdermal patches containing imipramine hydrochloride as model drug. Int J Pharm Pharm Sci. 2017 Jun 1;9(6):220. doi: 10.22159/ijpps.2017v9i6.16851.
18. Pastore MN, Kalia YN, Horstmann M, Roberts MS. Transdermal patches: history, development and pharmacology. Br J Pharmacol. 2015;172(9):2179-209. doi: 10.1111/bph.13059, PMID 25560046.
19. Jalhan S, Kaur K, Kaur P, K Jain U. Formulation and *in vitro* evaluation of transdermal matrix patches of doxophylline. Asian J Pharm Clin Res. 2016 Sep 1;9(5):140. doi: 10.22159/ajpcr.2016.v9i5.12774.
20. MA, Aa S, SP. Separation of flavonoids from alcoholic extract of Salvadora persica by HPLC. Int J Pharm Pharm Sci. 2013 Apr 1;5(Suppl 4):207–10.
21. Furuishi T, Io T, Fukami T, Suzuki T, Tomono K. Formulation and *in vitro* evaluation of pentazocine transdermal delivery system. Biol Pharm Bull. 2008 Jul; 31(7):1439–43.
22. Gutschke E, Bracht S, Nagel S, Weitschies W. Adhesion testing of transdermal matrix patches with a probe tack test-*in vitro* and *in vivo* evaluation. Eur J Pharm Biopharm. 2010 Aug;75(3):399-404. doi: 10.1016/j.ejpb.2010.03.016, PMID 20350598.
23. Patel B. Transdermal patch: A discrete dosage form. Int J Curr. 2011 Jan 1.
24. Pongjanyakul T, Prakongpan S, Priprem A. Acrylic matrix type nicotine transdermal patches: *in vitro* evaluations and batch-to-batch uniformity. Drug Dev Ind Pharm. 2003;29(8):843-53. doi: 10.1081/ddc-120024180, PMID 14570305.
25. Ahmed TA, Alay AMS, Okbazghi SZ, Alhakamy NA. Two-step optimization to develop a transdermal film loaded with dapoxetine nanoparticles: a promising technique to improve drug skin permeation. Dose-Response. 2020 Apr 1;18(2):1559325820923859. doi: 10.1177/1559325820923859, PMID 32425728.
26. Sharma S, Aggarwal G, Dhawan S. Design and evaluation of olanzapine transdermal patches containing vegetable oils as permeation enhancers. Der Pharmacia Lettre. 2010;2(6):84-98.
27. Gannu R, Vishnu YV, Kishan V, Rao YM. Development of nitrendipine transdermal patches: *in vitro* and ex vivo characterization. Curr Drug Deliv. 2007;4(1):69-76. doi: 10.2174/156720107779314767. PMID 17269919.
28. Patra JK, Das G, Fraceto LF, Campos EVR, Rodriguez Torres MDP, Acosta-Torres LS. Nano based drug delivery systems: recent developments and future prospects. J Nanobiotechnology. 2018;16(1):71. doi: 10.1186/s12951-018-0392-8, PMID 30231877.