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ELASTIC VESICLES FOR ENHANCING THE TRANSDERMAL DELIVERY OF OLMESARTAN MEDOXOMIL

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Hypertension seems to be a disorder that needs consideration for developing a transdermal drug delivery system (TDDS) because it requires long and continuing therapy. Olmesartan Medoxomil is an antihypertensive medication which has substantial first pass metabolism results in low oral bioavailability. In order to prevent oral complications, the production of elastic vesicles for improving Olmesartan Medoxomil transdermal distribution was the focus of this paper's study. Using a $2^1.3^1$ full factorial design and different edge activators in varying quantities, elastic vesicles formulas were created. The formulae's zeta potential (ZP), particle size (PS), polydispersity index (PDI), entrapment efficiency percentage (EE%), and amount of drug released after six hours (Q6h) were all described. Utilizing Design Expert® software, the ideal formula (F4) was determined, revealing EE% of 81.00±1.22%, PS of 287.30±1.43 nm, PDI of 0.18±0.03, ZP of -39.61±1.10 mV, and Q6h of 47.15±1.10%. The histological investigation verified the safety of the optimum elastic vesicles.

Keywords: *Olmesartan Medoxomil; elastic vesicles; factorial design; transdermal drug delivery*

INTRODUCTION

The biggest organ in the human body is thought to be the skin. It has benefits over other delivery methods from a pharmaceutical perspective, such as avoiding first-pass metabolism, fewer variations in plasma drug levels for repeated administration, and high patient compliance.[1]

However, owing to the characteristics of the skin, transdermal distribution presents a difficult method for the drug molecule to intrude on the appearance of its therapeutic function. The primary barrier to drug transit is the stratum corneum (SC), which has a thickness of 10 to 15 µm. The medications' physicochemical characteristics play a critical role in determining their capacity to traverse the SC, which requires pharmaceuticals with a molecular weight of less than 500 g/mol and a log P value of 1-3 to permeate.[2]

Olmesartan medoxomil has a restricted oral bioavailability of 26% and is classified as a class II drug in the Biopharmaceutics Classification System because of its significant first-pass metabolism and poor solubility. During absorption, ester hydrolysis bioactivates Olmesartan medoxomil to produce active olmesartan.

Further, Olmesartan medoxomil has been previously identified as a promising candidate for transdermal drug delivery. It has a molecular weight (MW) of 435.5 g/mol, a melting point of 184.14°C [3] and a biological half-life of 10-15 h.[4] Despite the many advantages of the skin as a site of drug delivery, only few drugs are currently available in the market as transdermal drug delivery system. This is because the inherent limitation of transdermal drug absorption which is imposed by the outermost layer of the skin the stratum corneum (SC).[5]

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Research has demonstrated that Olmesartan medoxomil 's effectiveness is significantly greater than several other recommended antihypertensive medications. Another method for administering Olmesartan medoxomil is to incorporate the medication into submicroscopic vesicles administered transdermally. This obscures the drug molecules and delivers the medication to the systemic circulation in a regulated fashion, so avoiding first pass metabolism.[6]

Olmesartan medoxomil has been included in several nanovesicles such as bilosomes containing sodium taurocholate and Brij surfactant.[7] Furthermore, another study performed for enhancing the transdermal permeability using vesicles of high malleability as transethosomes.[8] Moreover, Hathout et al fabricated nanoemulsion for enhancing Olmesartan medoxomil bioavailability and proved their speculation using pharmacokinetic studies on experimental animals. [9]

Phospholipid vesicles with an aqueous compartment surrounded by one or more lipid bilayers are known as liposomes. Many papers instead link liposomes to topical medication administration, despite the fact that only a small number of studies have explored the feasibility of transdermal drug delivery using liposomes. [10]

Cevec et al.[11] established a novel kind of liposomes called transferosomes as a drug delivery vehicle made up of an edge activator and phospholipid bilayer. The produced vesicles have flexibility due to the presence of edge activators, which reduces the likelihood of them rupturing, particularly when injected topically. Both hydrophobic and hydrophilic entities can surround medicinal molecules with a broad range of solubility within transferosomes. Without experiencing appreciable loss, it can flex and pass through the small constriction (between five and ten times smaller than its own diameter). This great deformability facilitates improved vesicle penetration.[12]

Furthermore, the vesicles' surfactant may cause the lipid and protein packing inside the SC to become unbalanced. Several studies have demonstrated that stiff liposomes were less successful than transferosomes for transdermal medication delivery. However, a number of investigations revealed that the transferosomes were unable to reach the stratum corneum's bottom layers.

Conversely, phospholipid and ethanol make up ethosomes, which were created by Touito et al.[13] Because ethanol interdigitates the lipid bilayer of vesicles, enhancing drug penetration through the skin, ethosomes can also improve the fluidity of lipids in the stratum corneum.[14]

Therefore, the current study's objectives were to assess the safety of elastic vesicles when applied to the skin, as well as the potential of these vesicles to increase Olmesartan Medoxomil's transdermal permeability. In order to do that, many factors affecting the features of vesicles were investigated using full factorial $2^1.3^1$ design and Design Expert® software to determine the ideal formulation.

Entrapment efficiency percentage (Y_1), particle size (Y_2), polydispersity index (Y_3), and zeta potential (Y_4) were chosen as dependent factors, and edge activator type (X_1) and amount (X_2) were examined as independent variables. The best elastic vesicles were assessed in terms of stability and shape. Additionally, male Wistar rats were used in histopathology investigations of Olmesartan Medoxomil from the ideal elastic vesicles.

MATERIALS AND METHODS

Olmesartan Medoxomil, Phospholipid from soya bean, Sodium deoxycholate (SDC), were purchased from Sigma Aldrich Chemical Co. (St. Louis, USA). Tween 80 (T80), chloroform, and methanol were obtained from El-Nasr Pharmaceutical Chemicals Co. (Cairo, Egypt).

Preparation of Olmesartan Medoxomil loaded elastic vesicles

Utilizing the thin film hydration approach, vesicles were created utilizing two edge activators, Tween 80 and Sodium deoxycholate, in different dosages (5, 15 and 25 mg). First, 10 milliliters of chloroform were used to dissolve the phospholipid (100 mg) and edge activator with Olmesartan Medoxomil (25 mg) in a long-necked, round-bottom flask. A thin clear coating of vesicles was generated by slowly evaporating the organic phase at 60°C using a rotatory evaporator (Rotavapor,

Heidolph VV 2000, Burladingen, Germany) at 90 rpm while keeping pressure under vacuum for 30 minutes. For 45 minutes, the film was hydrated with 10 mL of hydration media (bi-distilled water). To obtain mature vesicles, the vesicles dispersion was kept overnight at 4°C.[15]

Characterization and optimization of Olmesartan Medoxomil loaded elastic carriers Determination of entrapment efficiency percentage (EE%)

Using a cooling centrifuge (Sigma 3K 30, Germany), the vesicular dispersion for the prepared formulae was centrifuged at 20,000 rpm for 1 hour at 4°C. Next, methanol was used to lyse the pellet, and a UV-Vis spectrophotometer (Shimadzu UV1650 Spectrophotometer, Koyoto, Japan) was used to evaluate it at λ_{max} 257 nm. [9] EE% was found using the direct approach. [16]

Determination of particle size (PS), polydispersity index (PDI) and zeta potential (ZP)

Using a Malvern Zetasizer 2000 (Malvern Instruments Ltd., UK), the mean PS, PDI, and ZP of the vesicle's dispersions were calculated for the produced formulae. Following dilution, the measurements were carried out. By observing the particles' electrophoretic motion in the electrical field, the ZP evaluation was completed. Every measurement was done three times.[17]

Determination of amount of drug release

The shaking water bath was used for six hours at 37°C to measure the amount of medication released. Plastic cylindrical tubes with an area of 3.14 cm^2 were filled with 2 mL samples of the best elastic vesicles, each containing 5 mg of Olmesartan medoxomil. 50 mL of release media that composed of pH 7.4 phosphate buffer saline (PBS) (60%v/v) and 40 % ethanol (v/v) was used to submerge the formulations.[8] In this volume, the sink state was preserved. At 1, 2, 3, 4, 5, and 6 hours, aliquots were removed. A UV spectrophotometer with a λ_{max} of 257 [9] nm was used to evaluate aliquots of Olmesartan Medoxomil. Three experiments were carried out.

Assessment of the influence of different formulation parameters using $2^1.3^1$ full factorial design

Using minimum experimental runs, a complete $2^1.3^1$ full factorial design was employed to identify the impact of various factors on the characteristics of Olmesartan Medoxomil loaded elastic vesicles dispersions.[18] Two elements were assessed in the chosen design: one had two levels (X_1: edge activator type), and the other had three levels (X_2: edge activator amount). As dependent variables, the EE% (Y_1), PS (Y_2), PDI (Y_3), and ZP (Y_4) were identified **(Table 1).** To generate Olmesartan Medoxomil loaded elastic vesicles, all potential combinations were tried in the experiments **(Table 1)**. The experimental data were analyzed using Design Expert® software version 11 (Stat Ease, Inc., Minneapolis, Minnesota, USA) to independently source the major impacts of these components, and then analysis of variance (ANOVA) was used to determine the significance.

Table 1: $2^1.3^1$ Full factorial design for optimization of Olmesartan Medoxomil loaded elastic vesicles.

Factors (independent variables)	**Levels**		
X_1: Edge activator type	T80		SDC
X_2: Edge activator amount (mg)	5	15	25
Responses (dependent variables)	**Constraints**		
Y_1: EE (%)	Maximize		
Y_2: PS (nm)	Minimize		
Y_3: PDI	Minimize		
Y_4: ZP (mV)	Maximize		

Abbreviations: EE%; entrapment efficiency percent, PS; particle size, PDI; polydispersity index, and ZP; zeta potential.

Optimization of Olmesartan Medoxomil loaded elastic vesicles

The desirability function which predicts the optimal levels of selected components was developed in order to identify the best formulation to be chosen for additional research. Achieving the lowest PS and PDI and the highest EE% and ZP (as absolute value) were the criteria established for choosing the best formulation.

Transmission electron microscopy (TEM)

Using a transmission electron microscope (Joel JEM 1230, Tokyo, Japan), the morphology of the ideal elastic vesicles was investigated. A thin layer of the vesicular dispersion was applied to a copper grid covered with carbon, dyed with 1.5% phosphotungstic acid, and observed. and photographed.[19]

Differential scanning calorimetry (DSC)

Through the use of purified indium as a calibration, differential scanning calorimetry (DSC-60, Shimadzu Corp., Kyoto, Japan) was used to undertake a thermal examination of both the ideal elastic vesicles and pure Olmesartan Medoxomil. Each sample, weighing about 5 mg, was placed in typical aluminum pans and heated between 10 and 250°C at a scanning rate of 5°C per minute while an inert nitrogen flow was in place (25 mL/min).[20]

Stability studies

Optimum elastic vesicles were stored at 4°C 45 days. Samples from each formulation were withdrawn at 0 and 45 days. Stability was evaluated by comparing the initial measurements with results obtained after storage. The EE%, PS, PDI, ZP and Q6h (%) from the vesicles were measured as described previously. Statistical significance was analyzed by Student's t-test using SPSS® software 22.0. Difference at $p \leq 0.05$ was considered significant.[21]

Histopathological study

The study design was approved by the ethical committee of the Mazaya University College, (reference number = (PI) 105). Animals were divided into two groups where group one acted as control, while group two was treated with the optimum elastic vesicles. The treatment period lasted one day. After being fixed for 24 hours in 10% formol saline, skin samples were cleaned, and alcohol was used to dehydrate them. Following a 24-hours period at 56°C, the specimens were cleaned in xylene, embedded in paraffin wax blocks, and sectioned using a sledge microtome (Rotary Leica RM2245, USA) at a thickness of 4 mm. Using light microscopy, the specimens were deparaffinized and stained with hematoxylin and eosin stains for histological analysis. (Axiostar plus, Zeiss, New York, NY).[22]

RESULTS AND DISCUSSION

Results

Analysis of factorial design

Two independent variables were studied: the edge activator type (X_1) and edge activator amount (mg) (X_2); dependent variables included EE% (Y_1), PS (Y_2), PDI (Y_3), and ZP (Y_4). The experimental results were analyzed using Design Expert® software (Stat Ease, Inc., Minneapolis, MN) version 11 to source independently the main effects of these factors, which were then analyzed using analysis of variance (ANOVA) to determine the significance of each factor. The two-factor interaction (2 FI) model was used, and it was seen that the anticipated R^2 values were in reasonable agreement with the adjusted R^2 in all responses, with reference to the design analysis results in **Table 2**. The overall mean is a more accurate predictor of the reaction, according to the PDI's anticipated R^2 value, which is negative. Referring to design analysis results in **Table 2**, the model selected was two-factor interaction (2FI) and it was noted that the predicted R^2 values were in reasonable agreement with the adjusted R^2 in all responses results can be shown in **Table2**, all responses exhibited acceptable adequate precision with a ratio larger than 4.

The effect of formulation variables on EE%

Depending on the lipid composition and qualities, encapsulating bioactive inside phospholipid formulations provides the optimal delivery, improved stability, protection, and permeability.[23] The effect of the independent variables, edge activator type (X_1) and edge activator amount (mg) (X_2) on the EE% of Olmesartan Medoxomil in elastic vesicles is

shown in **Table 2,3** and is graphically illustrated as 3-D surface plots in **Fig. 1A.** It is observed that edge activator type (X_1) had a significant effect on EE% ($p<0.0001$).

When comparing Tween 80-containing formulas to SDC formulations, the EE% was greater. This is consistent with the findings of Aboud et al. and could be explained by the edge activators' HLB values, which are, respectively, 15 and 23.4 for T80 and SDC.[24] It is commonly recognized that lipophilic drugs would be better entrapped by edge activators with lower HLB values since they are more lipophilic.[25]

This explains why formulations including Tween 80 had higher EE% of Olmesartan Medoxomil, a highly lipophilic medication with a log P value of 5.6. Moreover, Tween 80's extremely hydrophobic alkyl chains interact with the vesicles' hydrophobic domain to produce more compacted vesicle layers, which stops drugs from leaching from vesicles.[24]The EE% of Olmesartan Medoxomil would decrease, however, if edge activators with higher hydrophilicity, such as SDC, formed fewer stiff vesicles because of their bigger polar head groups and greater drug solubilization in the aqueous medium during production.[26]

Regardless of the type of edge activators, the edge activator's EE% was maximum at 5 mg, but at 25 mg, the drug's EE% was drastically reduced. The findings corroborated those of Ezzat et al.,[27] who found that EE% fell as phospholipid concentration dropped. This might be explained by a reduction in the amount of space available for drug loading into the vesicles.[8]

Table 2: Output data of the $2^1.3^1$ full factorial analysis of elastic vesicles formulations and predicted and observed values for the optimum elastic vesicles.

Responses	EE%	PS (nm)	PDI	ZP (mV)
Adjusted R^2	0.999	0.999	0.996	0.944
Predicted R^2	0.998	0.999	0.991	0.988
Adequate precision	143.22	490.83	52.23	60.00
Significant factors	X_1, X_2	X_1, X_2	X_1, X_2	X_1, X_2
Predicted value of optimum formula	81.00	287.16	0.185	-39.90
Observed value of optimum formula	80.60	287.31	0.182	-39.00

Abbreviations: EE%, entrapment efficiency percentage; PS, particle size; PDI, polydispersity index; and ZP, zeta potential.

Table 3: Experimental runs, independent variables, and measured response of the $2^1.3^1$ full factorial experimental design of elastic vesicles.

	Edge activator type	Edge activator amount (mg)	EE%	PS (nm)	PDI	ZP (mV)
F1	T80	5	81.00±2.00	411.00±2.00	0.040±0.001	-31.00±1.00
F2	T80	15	80.98±1.89	387.00±3.00	0.210±0.120	-30.50±1.50
F3	T80	25	77.00±1.00	338.00±2.00	0.030±0.001	-24.30±1.20
F4	SDC	5	81.00±1.23	287.90±2.10	0.180±0.002	-39.60±1.23
F5	SDC	15	59.00±0.12	232.00±2.00	0.150±0.003	-34.00±2.00
F6	SDC	25	54.00±1.00	215.00±3.00	0.020±0.100	-28.00±2.00

Note: Data represented as mean ± SD (n=3).
Abbreviations: EE%, entrapment efficiency percentage; PS, particle size; PDI, polydispersity index and ZP, zeta potential

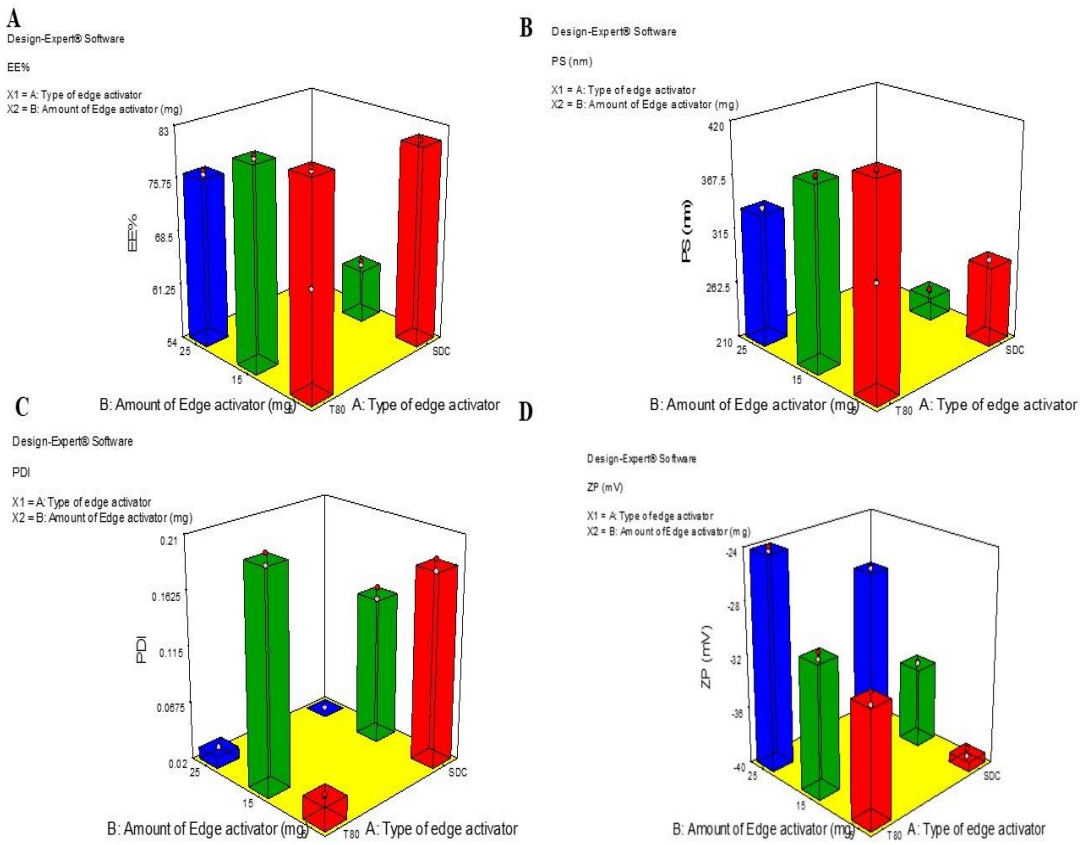

Fig. 1: Effect of edge activator type (X_1) and edge activator amount (X_2) on EE%, PS, PDI, and ZP of elastic vesicles.

The effect of formulation variables on PS

The z-average diameter, which indicates the particles' mean hydrodynamic diameter [27] was measured and presented in **Table2,3** and graphically illustrated in 3-D surface plots **(Fig. 1B).** It is noticeable that both edge activator type (X_1) and edge activators amount (mg) (X_2), influenced significantly ($p<0.0001$) the PS of the vesicles. The PS for formulae prepared by Tween 80 was higher than that of identical formulations prepared by other edge activators, taking into account the type of edge activator. Yeo et al.[28] reported that a decrease in the hydrophilic component of SAA is connected to an increase in the PS of vesicles when the edge activator HLB value drops. As a result, Tween 80, which had the lowest HLB value (18), produced the highest PS. Furthermore, compared to the similar formulations prepared with SDC, the Tween 80-made formulae with an alkyl chain length of 18 carbon atoms displayed greater vesicular diameters. However, due to steric repulsion between the charged molecules exposed from the vesicle membrane's outer layer, the smallest vesicles were produced when anionic SDC was incorporated into the vesicle bilayer. As a result, the vesicles would be smaller due to an increase in the curvature of the vesicle membrane. Furthermore, as was already indicated, the modest PS was also explained by the high HLB value of SDC (23.4).[25]

Comparing the edge activator amount at 25 ratios to the other 2 ratios, it produced the smallest PS with regard to edge activator amount (mg) (X_2) ($p<0.0001$). Phospholipids are known to have a cylindrical form due to the size of their hydrophobic tails. Furthermore, the amphiphilic head group of the edge activators molecule requires more space than the hydrophobic tail's cross section area, which is why the molecule resembles a cone. The hydrophobic tails of the cone-shaped edge activators insert into the lipid bilayers and engage with the lipid polar fragments through their head groups. This process occurs when the edge activators interact with lipid bilayers. Lipid edge activators aggregates become more curved as the amount of edge activators grows because of the difference in the hydrophobic

chain lengths of phospholipid and edge activators. Thus, the PS is reduced as a result of the cone-shaped edge activators' disruption of the densely packed lipid bilayers. The data also showed that, for every formula, the PS matched the quantity of medication entrapped in the vesicles. Consequently, the decline in EE% would provide an additional rationale for the reduced PS of vesicles.[29]

The effect of formulation variables on PDI

The width of unimodal size distributions is measured by the PDI. Further, PDI was measured and presented in **Table 2,3** and graphically illustrated in 3-D surface plots **(Fig. 1C).** A homogeneous dispersion is indicated by a value of 0, whereas a completely heterogeneous polydisperse population is indicated by a value of 1. Factorial analysis of variance showed that both independent variables, edge activator type (X_1) and edge activator amount (X_2), showed significant effect on PDI with p values of ($p<0.0001$) for both factors. A PDI that is considered acceptable should be less than 0.5. The produced vesicles' polydispersity indices were often minimal, as can be seen from the data, indicating strong homogeneity and a narrow size distribution. [30]

The effect of formulation variables on ZP

Because of electrostatic repulsion, charged vesicles with a ZP of ($\geq|30|$mV) are less likely to aggregate.[31] As demonstrated in **Table 2,3** and visually represented as response 3-D graphs in **Fig. 1D**, the ANOVA findings indicated that both independent variables edge activator type (X_1) and edge activator amount (mg) (X_2) showed a significant effect on ZP ($p<0.0001$). It was shown that utilizing Tweens instead of SDC reduced the ZP of vesicles. More OH ion adsorption will take place at the surfactant with a lower HLB value (a more nonpolar interface), which will lead to an increase in ZP. Furthermore, Tweens' $(CH_2\text{-}CH_2\text{-}O)_n$ created hydrogen bonds with water molecules, which decreased ZP values. [32]

In addition, when compared to other tweens, the addition of anionic SDC produced the greatest ZP values. Following ionization in water, SDC produces an electric double layer by being adsorbed on the particle/water contact. Furthermore, non-ionic edge activators produce lower ZP because they have a more significant impact on spreading the diffuse layer. Anionic edge activators, on the other hand, are held up more firmly around the particle and as a result have less of an impact on the diffuse layer's thickness, maintaining greater ZP values.[33]

With respect to edge activator amount (X_2), vesicles with the lowest amount of surfactant exhibited the most negative ZP. Although, phospholipid heads cause the negative ZP value in water even though they are zwitterionic and so technically uncharged at neutral pH. Makino et al.[34] proposed that the direction of the dipole joining the positive charge of the choline group and the negative charge of the phosphatidyl group in a lipid molecule's head group is responsible for the charge of the phospholipid bilayer. According to a report, the head group is orientated so that the phosphatidyl group is outside and the choline group is inside in a medium with low ionic strength, producing a negative surface charge.

Selection of the optimized formulation

A set of criteria was first established in the Design Expert® software (Stat Ease, Inc., Minneapolis, MN) version 11 in order to choose the best formula. Particles having the highest EE%, ZP (absolute value), and lowest PS and PDI were given preference according to these parameters. The primary effects of these parameters were separately found through the use of Design Expert® to examine the experimental data. An analysis of variance (ANOVA) was then performed to ascertain the importance of each element. The formula that satisfied the predetermined criteria was the best one. The ideal elastic vesicles had a ZP of -39.60±1.23 mV, PDI of 0.180±0.002, PS of 287.90±2.10 nm, and EE% of 81.00±1.23%. The expected and observed responses of were compared and are displayed in **Table 2** to verify the validity of our experiment. There was a strong correlation found between the actual and anticipated values for the optimum formula F4 that contained 5 mg SDC.

Characterization of the optimum formula

***In-vitro* drug release**

When predicting a drug's *in-vivo* performance, the release profile is a crucial

indicator. High surface area and a faster rate of disintegration are the outcomes of PS decrease.[35] Q6h for the optimum elastic vesicles and Olmesartan Medoximil suspension is displayed in **Fig. 2**. Additionally, the results indicated that the optimum elastic vesicles containes SDC that provides higher release percent compared to Olmesartan Medoximil suspension. This is likely due to the fact that SDC created the small PS vesicles, increasing the total surface area and, thus, the release rate.[24] Furthermore, the inclusion of SDC led to the formation of mixed micelles including phospholipid and improved Olmesartan Medoximil's aqueous solubility in the aqueous phase.[36]

Morphology of vesicles

TEM examination was used to examine the external morphology of the obtained optimum elastic vesicles formulation. Elastic vesicles' morphological shape revealed that they were spherical and had a consistent size distribution **(Fig. 3).** The Zetasizer-determined vesicle sizes did match the TEM data fairly well.

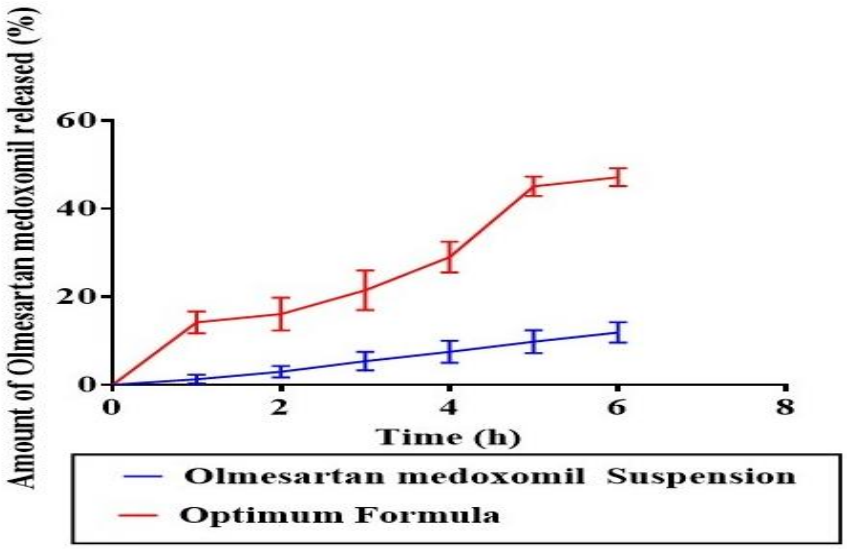

Fig. 2: *In-vitro* drug release for Olmesartan Medoxomil and the optimum formula.

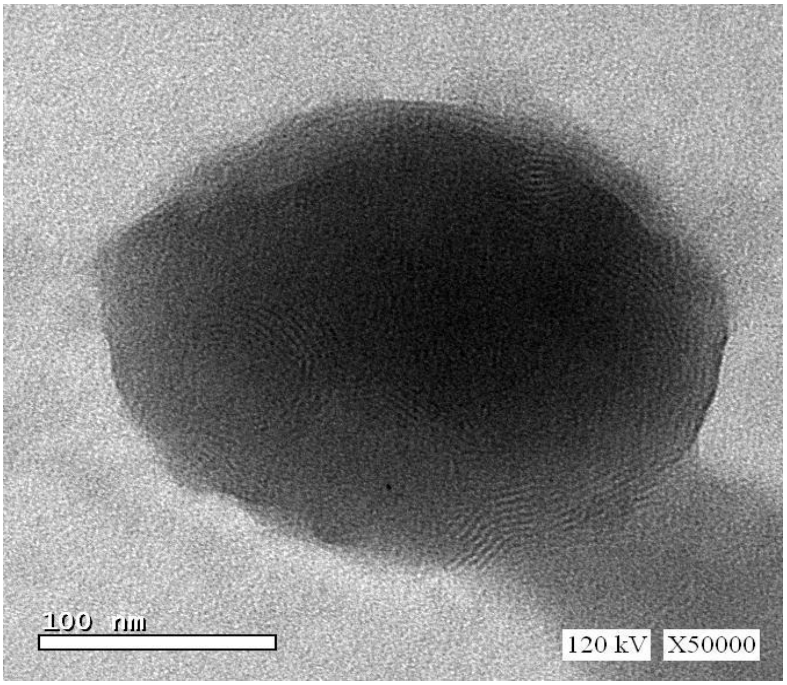

Fig. 3: Transmission electron micrograph for the optimum elastic vesicles.

Differential scanning calorimetry (DSC)

The ideal elastic vesicles and pure Olmesartan Medoxomil thermograms are displayed in the **Fig. 4**. Pure Olmesartan Medoxomil's DSC scan revealed a single endothermic peak at 184.14°C.[37] Drug entrapment in vesicles may be indicated by the absence of the drug's distinctive peak in the optimal elastic vesicle's DSC thermogram. Hydrogen bond formation, Van der Waals attractive forces, or dipole-dipole forces at the drug's hydroxyl groups as well as those of the phospholipid and SDC are likely examples of these interactions. The development of a vesicle with an advantageous shape and structure that has good stability. [38]

Stability study

During storage, lipid vesicular formulations have a tendency to fuse and disintegrate, changing PS, PDI, and ZP. Additionally, these modifications result in a decrease in the EE% and medication leakage from the vesicles.[39] Vesicles were visually inspected for aggregation and appearance changes. Furthermore, it was determined what EE% of 82.00±1.62%, PS of 289.70±3.13 nm, PDI of 0.19±0.05, ZP of -38.71±2.10 mV, and Q6h of 48.15±2.10%. After 45 days at 4°C, statistical analysis showed that there was no discernible change between the fresh and preserved vesicles in terms of EE%, PS, PDI, ZP and Q6h. These results suggest that the ideal elastic vesicles are stable.

Histopathological study

Permeation enhancers are thought to be a key barrier to transdermal delivery due to skin irritation.[40] When compared to untreated skin sections (group I), light microscopy analysis of groups II which were treated with the optimum elastic vesicles, respectively, revealed no histological alterations in epidermal and dermal cells **(Fig. 5).** These results showed that the ideal elastic vesicles had a tolerable level of acceptability.

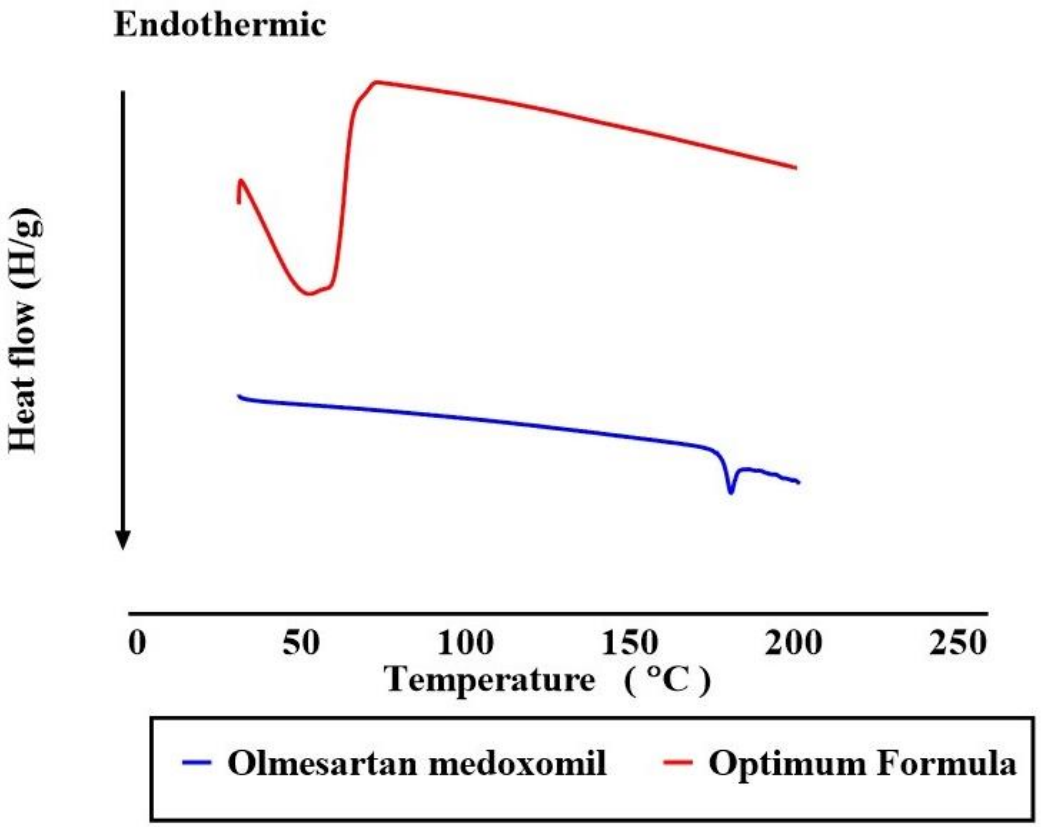

Fig. 4: Differential scanning colorimetry for Olmesartan Medoxomil and the optimum formula.

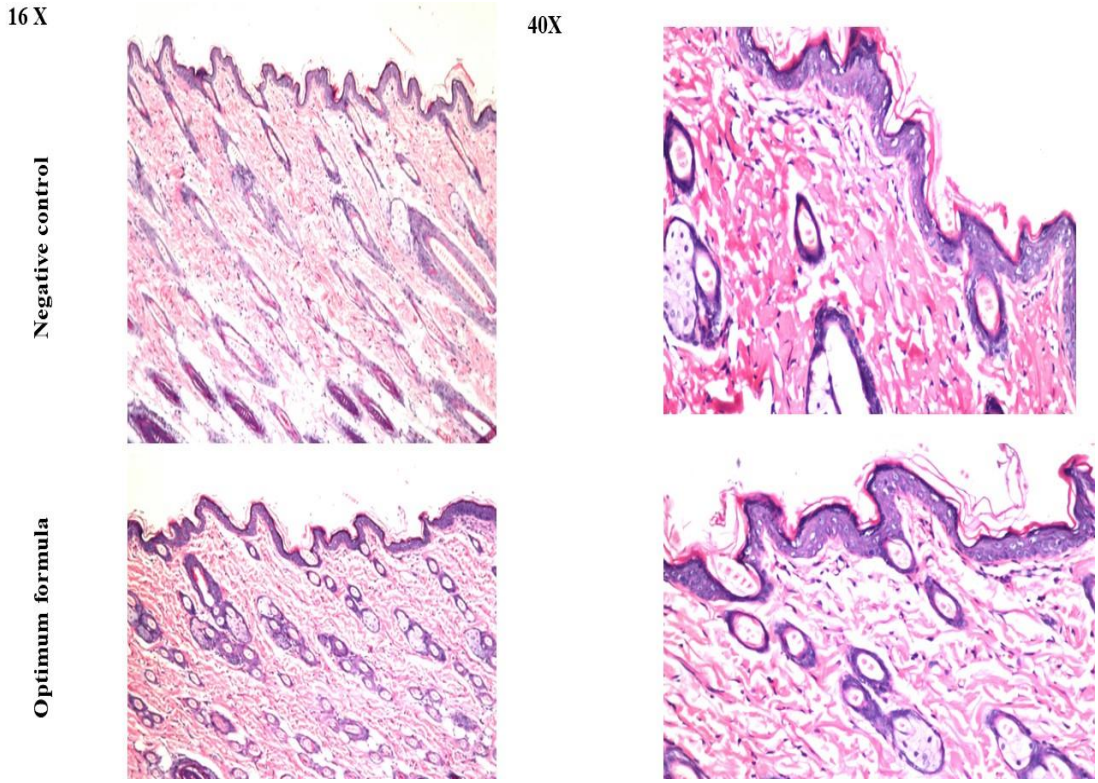

Fig. 5: Histopathological study for the optimum elastic vesicles compared to the negative control.

Conclusion

In this study, we developed elastic vesicles as a transdermal Olmesartan Medoxomil delivery method. In accordance with the $2^1.3^1$ full factorial design, six formulations were created using the thin film hydration process. These formulations were then utilized to choose the best elastic vesicles, which had spherical morphology, a good drug EE%, minimal PS, high Olmesartan Medoxomil release percent, and good ZP values. Additionally, DSC experiments on elastic vesicles verified that Olmesartan Medoxomil was entrapped within the structure of the vesicles. Additionally, the *in-vivo* histological investigation verified that optimum elastic vesicles did not cause irritation when applied to rat skin. The findings therefore indicated that, since elastic vesicles bypass Olmesartan Medoxomil's significant first pass metabolism and do not cause oral issues, they could be regarded as a potential transdermal administration strategy. To prove that elastic vesicles are therapeutically effective in humans, more research is required.

REFERENCES

1. M. Chen, X. Liu and A. Fahr, "Skin penetration and deposition of carboxyfluorescein and temoporfin from different lipid vesicular systems: In vitro study with finite and infinite dosage application", ***Int J Pharm***, 15, 408(1–2), 223–234 (2011).
2. N. Ø. Knudsen, S. Rønholt, R. D. Salte, L. Jorgensen, *et al.*, "Calcipotriol delivery into the skin with PEGylated liposomes", ***Eur J Pharm Biopharm,*** 81(3), 532–539(2012).
3. K. Nagaraj, D. Narendar and V. Kishan, "Development of olmesartan medoxomil optimized nanosuspension using the Box–Behnken design to improve oral bioavailability", ***Drug Dev Ind Pharm***, 43(7), 1186–1196(2017).
4. M. Kamran, A. Ahad, M. Aqil, S. S. Imam, Y. Sultana and A Ali., "Design, formulation and optimization of novel soft nano-carriers for transdermal olmesartan medoxomil delivery: In vitro characterization and in vivo

pharmacokinetic assessment", ***Int J Pharm,*** 505(1–2), 147–158 (2016).

5. N. M. Morsi, A. A. Aboelwafa and M. H. S. Dawoud, "Improved bioavailability of timolol maleate via transdermal transfersomal gel: Statistical optimization, characterization, and pharmacokinetic assessment", ***J Adv Res***, X 7(5), 691–701(2016).
6. J. M. Alsofany, M. Y. Hamza, A. A. Abdelbary, "Fabrication of nanosuspension directly loaded fast-dissolving films for enhanced oral bioavailability of olmesartan medoxomil: in vitro characterization and pharmacokinetic evaluation in healthy human volunteers", ***AAPS PharmSciTech***, 19(5), 2118–2132(2018).
7. R. Albash, M. A. El-Nabarawi, H. Refai and A. A. Abdelbary, "Tailoring of PEGylated bilosomes for promoting the transdermal delivery of olmesartan medoxomil: Invitro characterization, ex-vivo permeation and in-vivo assessment", ***Int J Nanomedicine,*** 14, 6555–6574 (2019).
8. R. Albash, A. A. Abdelbary, H. Refai and M. A. El-Nabarawi, "Use of transethosomes for enhancing the transdermal delivery of olmesartan medoxomil: In vitro, ex vivo, and in vivo evaluation", ***Int J Nanomedicine***, 14, 1953–1968(2019).
9. R. M. Hathout, A. H. Elshafeey, "Development and characterization of colloidal soft nano-carriers for transdermal delivery and bioavailability enhancement of an angiotensin II receptor blocker", ***Eur J Pharm Biopharm***,82(2), 230–240 (2012).
10. M. Ashtikar, K. Nagarsekar and A. Fahr, "Transdermal delivery from liposomal formulations – Evolution of the technology over the last three decades", ***J Control Release***, 242, 126–140 (2016).
11. G. Cevc, A. Schätzlein, H. Richardsen, "Ultradeformable lipid vesicles can penetrate the skin and other semi-permeable barriers unfragmented. Evidence from double label CLSM experiments and direct size measurements", ***Biochim Biophys Acta – Biomem,*** 1564(1), 21-30(2002).
12. A. H. Al-Shuwaili, B. K. A. Rasool and A. A. Abdulrasool, "Optimization of elastic transfersomes formulations for transdermal delivery of pentoxifylline", ***Eur J Pharm Biopharm,*** 102, 101–114 (2016).
13. E. Touitou, B. Godin, N. Dayan, C. Weiss, A. Piliponsky and F. Levi-Schaffer, "Intracellular delivery mediated by an ethosomal carrier", ***Biomaterials***, 22(22),3053-3039(2001).
14. R. G. S. Maheshwari, R. K. Tekade, P. A. Sharma, G. Darwhekar, *et al.*, "Ethosomes and ultradeformable liposomes for transdermal delivery of clotrimazole: A comparative assessment", ***Saudi Pharm J,*** 20(2), 161–170 (2001).
15. R. Albash, N. M. Badawi, M. I. A. Hamed, M. H. Ragaie, S. S. Mohammed, *et al.*, "Exploring the synergistic effect of bergamot essential oil with spironolactone loaded nano-phytosomes for treatment of acne vulgaris: in vitro optimization, in silico studies, and clinical evaluation", ***Pharmaceuticals,*** 16(1), 128 (2001).
16. H. Refai, A. A. El-Gazar, G. M. Ragab, D. H. Hassan, *et al.*, "Enhanced Wound Healing Potential of Spirulina platensis Nanophytosomes: Metabolomic Profiling, Molecular Networking, and Modulation of HMGB-1 in an Excisional Wound Rat Model", ***Mar Drugs,*** 21(3), 149 (2023).
17. H. R. H. Mohamed, S. El-Shamy, S. S. Abdelgayed, R. Albash and El-Shorbagy, "Modulation efficiency of clove oil nano-emulsion against genotoxic, oxidative stress, and histological injuries induced via titanium dioxide nanoparticles in mice", ***Sci Rep***, 14(1), 7715 (2024).
18. R. Albash, M. M. Abdellatif, M. Hassan and N. M. Badawi, "Tailoring terpesomes and leciplex for the effective ocular conveyance of moxifloxacin hydrochloride (Comparative assessment): In-vitro, ex-vivo, and in-vivo evaluation", ***Int J Nanomedicine,*** 16, 5247–5263(2021).
19. M.A. Eltabeeb, R. R. Hamed, M. A. El-Nabarawi, M. H. Teaima, *et al.*, "Nanocomposite alginate hydrogel loaded

with propranolol hydrochloride kolliphor® based cerosomes as a repurposed platform for Methicillin-Resistant Staphylococcus aureus-(MRSA)-induced skin infection; in-vitro, ex-vivo, in-silico, and in-vivo evaluation", ***Drug Deliv Transl Res***, 18, (2024).

20. Y. Elmahboub, R. Albash, M. M. William, A. H. Rayan, *et al.*, "Metformin Loaded Zein Polymeric Nanoparticles to Augment Antitumor Activity against Ehrlich Carcinoma via Activation of AMPK Pathway: D-Optimal Design Optimization, In Vitro Characterization, and In Vivo Study", ***Molecules,*** 29(7), 1614 (2024).
21. M. H. Teaima, M. A. Eltabeeb, M. A. El-Nabarawi and M. M. Abdellatif., "Utilization of propranolol hydrochloride mucoadhesive invasomes as a locally acting contraceptive: in-vitro, ex-vivo, and in-vivo evaluation", ***Drug Deliv***, 29(1), 2549–2560 (2022).
22. D. E. Aziz, A. A. Abdelbary and A. I. Elassasy, "Investigating superiority of novel bilosomes over niosomes in the transdermal delivery of diacerein: in vitro characterization, ex vivo permeation and in vivo skin deposition study", ***J Liposome Res***, 29(1), 73–85 (2019).
23. A. C. Mendes, C. Gorzelanny, N. Halter, S. W. Schneider and I. S. Chronakis, "Hybrid electrospun chitosan-phospholipids nanofibers for transdermal drug delivery", ***Int J Pharm***, 510(1), 48–56(2016).
24. H. M. Aboud, A. A. Ali, S. F. El-Menshawe, A. A. Elbary, "Nanotransfersomes of carvedilol for intranasal delivery: formulation, characterization and in vivo evaluation", ***Drug Deliv***, 23(7), 2471–2481(2016).
25. H. Kunieda and K. Ohyama, "Three-Phase Behavior and HLB Numbers of Bile Salts and Lecithin in a Water-Oil System", ***J colloid Interf Sci,*** 136(2), 432-439(1990).
26. V.B. Junyaprasert, P. Singhsa, J. Suksiriworapong and D. Chantasart,"Physicochemical properties and skin permeation of Span 60/Tween 60 niosomes of ellagic acid", Int J Pharm. 28;423(2):303–11 (2012).
27. S. M. Ezzat, M. M. Salama, A. N. ElMeshad, M. H. Teaima, L. A. Rashad, "HPLC–DAD–MS/MS profiling of standardized rosemary extract and enhancement of its anti-wrinkle activity by encapsulation in elastic nanovesicles", ***Arch Pharm Res***, 39(7), 912–925 (2016).
28. L. K. Yeo, T. O. B. Olusanya, C. S. Chaw, A. A. Elkordy, "Brief effect of a small hydrophobic drug (Cinnarizine) on the physicochemical characterisation of niosomes produced by thin-film hydration and microfluidic methods", ***Pharmaceutics,*** 10(4), 185 (2018).
29. Y. Chen, F. Qiao, Y. Fan, Y. Han and Y. Wang, " Interactions of Cationic/Anionic Mixed Surfactant Aggregates with Phospholipid Vesicles and Their Skin Penetration Ability", ***Langmuir,*** 33(11), 2760–2769(2017).
30. A. H. Salama and M. H. Aburahma., "Ufasomes nano-vesicles-based lyophilized platforms for intranasal delivery of cinnarizine: preparation, optimization, ex-vivo histopathological safety assessment and mucosal confocal imaging", ***Pharm Dev Technol,*** 21(6),706–715 (2016).
31. R. M. Khalil, G. A. Abdelbary, M. Basha, G. E. A. Awad, H. A. el-Hashemy,"Enhancement of lomefloxacin Hcl ocular efficacy via niosomal encapsulation: in vitro characterization and in vivo evaluation" J Liposome Res. 27(4), 312–323(2017).
32. N. Ibrahim, I. Ab-Raman and M. R. Yusop, "Effects of functional group of non-ionic surfactants on the stability of emulsion malaysian palm oil board effects of functional group of non-ionic surfactants on the stability of emulsion", ***Malaysian J Anal Sci,***19(1), 261-267 (2015).
33. U. Nagaich and N. Gulati, "Nanostructured lipid carriers (NLC) based controlled release topical gel of clobetasol propionate: design and in vivo characterization", ***Drug Deliv Transl Res,*** 6(3), 289–298(2016).
34. K. Makino, T. Yamada, M. Kimura, T. Oka, H. Ohshima and T. Kondo, "Temperature-and ionic strength-induced

conformational changes in the lipid head group region of liposomes as suggested by zeta potential data" Biophysical chemistry, 41(2), 175-183 (1991).
35. M. M. Abdellatif, I. A. Khalil and M. A. F. Khalil, "Sertaconazole nitrate loaded nanovesicular systems for targeting skin fungal infection: In-vitro, ex-vivo and in-vivo evaluation", ***Int J Pharm,*** 527(1–2),1–11 (2017).
36. A. M. Al-Mahallawi, A. A. Abdelbary and M. H. Aburahma, "Investigating the potential of employing bilosomes as a novel vesicular carrier for transdermal delivery of tenoxicam", ***Int J Pharm,*** 485(1–2), 329–340(2015).
37. R. Albash, M. A. El-Nabarawi, H. Refai and A. A. Abdelbary, "Tailoring of PEGylated bilosomes for promoting the transdermal delivery of olmesartan medoxomil: Invitro characterization, ex-vivo permeation and in-vivo assessment", ***Int J Nanomedicine,*** 14, 6555–6574(2019).
38. M. M. El-Naggar, M. A. El-Nabarawi, M. H. Teaima, *et al.*, "Integration of terpesomes loaded Levocetrizine dihydrochloride gel as a repurposed cure for Methicillin-Resistant Staphylococcus aureus (MRSA)-Induced skin infection; D-optimal optimization, ex-vivo, in-silico, and in-vivo studies", ***Int J Pharm***, 25, 633(2023).
39. A. Zeb, O. S. Qureshi, H. S. Kim, J. H. Cha, H. S. Kim and J. K. Kim, "Improved skin permeation of methotrexate via nanosized ultradeformable liposomes", ***Int J Nanomedicine,*** 11, 3813–3824(2016).
40. K. Priyanka and S. Singh, "A Review on skin targeted delivery of bioactives as ultradeformable vesicles: overcoming the penetration problem", ***Curr Drug Targets,*** 15(2), 184–198(2014).

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الحويصلات المرنة لتعزيز توصيل أولميسارتان ميدوكسوميل عبر الجلد

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يبدو أن ارتفاع ضغط الدم هو اضطراب يحتاج إلى دراسة لتطوير نظام توصيل الدواء عبر الجلد (TDDS) أنه يتطلب علاجًا طويلًا ومستمرًا. أولميسارتان ميدوكسوميل هو دواء خافض لضغط الدم وله استقلاب أولي كبير يؤدي إلى انخفاض التوافر البيولوجي عن طريق الفم. من أجل منع المضاعفات الفموية، كان إنتاج الحويصلات المرنة لتحسين توزيع أولميسارتان ميدوكسوميل عبر الجلد هو محور دراسة هذه الورقة. باستخدام التصميم العاملي الكامل ٢١,٣١ ومجموعة من منشطات الحواف بكميات مختلفة، تم إنشاء صيغ الحويصلات المرنة. تم وصف إمكانات زيتا للصيغة (ZP)، وحجم الجسيمات (PS)، ومؤشر تعدد التشتت (PDI)، ونسبة كفاءة الانحباس (EE٪)، وكمية الدواء المنطلق بعد ست ساعات (Q6h). باستخدام برنامج Design Expert®، تم تحديد الصيغة المثالية (F4)، التي كشفت عن EE% بنسبة ٨١,٠٠±١,٢٢%، PS بمقدار ٢٨٧,٣٠±١,٤٣ نانومتر، PDI بمقدار ٠,١٨±٠,٠٣، ZP بمقدار −٣٩,٦١±١,١٠ مللي فولت، وQ6h بمقدار ٤٧,١٥± ١,١٠%. التحقق النسيجي من سلامة الحويصلات المرنة المثلى البحث.