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ABSTRACT

Valsartan (VAL) is used as a first-line agent to treat hypertension. However, VAL exhibits poor absorption and low bioavailability when administrated orally. To overcome these issues, VAL transdermal gel was developed in this study, where Carbopol was used as the gel matrices. Additionally, solid microneedles (Dermaroller®) with various needle lengths were combined with transdermal gel to improve its permeation across the stratum corneum as a skin barrier. Developed formulations were further evaluated for various parameters, including pH, viscosity, spreadability, extrudability, gel strength, drug content, *ex vivo* permeation, *in vitro* release, occlusivity, and hemolysis. The results showed that all formulations exhibited desired physical characteristics without any potential to cause toxicity. Moreover, this approach showed that using microneedles could significantly enhance the permeation of VAL up to 3 folds compared to untreated skin. The use of microneedles 1.5 mm was found to be the optimum combination to improve VA permeation without affecting skin integrity. As much as 1.69 ± 0.004 mg of VAL permeated after 8 h. Finally, it could be concluded that this work had successfully developed a new approach for VALS drug delivery and could potentially show a significant impact on the treatment of hypertension. Further *in vivo* work should be considered.

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KEYWORDS
Valsartan; polymeric hydrogel; transdermal delivery; solid microneedles

1. Introduction

Hypertension is a condition characterized by high blood pressure (BP) in the systemic arteries, expressed by the ratio of systolic and diastolic BP [1]. Hypertension is defined as having systolic BP 140 mmHg or higher and/or having diastolic BP 90 mmHg or higher [2]. It is a major global health problem due to its high prevalence. Around 12.8% (7.5 million) of the total of all annual deaths worldwide were

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caused by high BP and it is predicted to increase to 1.56 billion adults with hypertension in 2025 [3]. It is also a significant risk factor for cardiovascular disease (CVD) and chronic kidney disease (CKD) and is the single leading contributor to all-cause death and disability worldwide [4].

Valsartan (VAL) is an antihypertensive drug which belongs to angiotensin II receptor blocker (ARB). The use of VAL does not associate with persistent cough/angioedema due to its ability to not inhibit the breakdown of bradykinin. According to Nixon et al. [5], among other ARB drugs, VAL is found to be more effective at lowering BP and shows comparable efficacy in patients. However, when administrated orally, VAL exhibits low bioavailability (around 10–35%) due to poor absorption in the gastrointestinal tract. Furthermore, food intake is known to affect the pharmacokinetics of VAL by reducing its C_{max} and AUC [6, 7]. Therefore, finding an alternative route for delivering VAL is needed.

Transdermal drug delivery system (TDDS) is an alternative drug delivery that offers various advantages. It can increase drugs' bioavailability, avoid hepatic first-pass metabolism, provide a non-invasive route for the patient, and reduce dosing frequency, thus improving patient compliance. In addition, TDDS can be self-administrated and generally inexpensive [8, 9]. Moreover, because patients with hypertension need long term treatment, TDDS provide a more convenient and acceptable route [7]. Gels can provide an advantage in delivering VAL *via* the transdermal route because gels tend to be softer, non-greasy, offer a cooling effect and provide a better drug release effect than other semisolid dosage forms [10]. Carbopol is one of the polymers that can be used as a gel base because it can increase the viscosity of preparations with low concentrations and can be combined with many active substances. A study by Patel et al. [11] showed that Carbopol-based gel exhibits better drug release than other gel bases.

VAL is a promising candidate to be successfully delivered by transdermal route by having a low molecular weight (434.5 Da) and melting point below 200 °C (116–117 °C) [12]. Moreover, there are no reports of skin irritation caused by VAL [13]. Nevertheless, the log partition coefficient (log *P*) of VAL is too high (4.5), which limits its permeation through the skin. High log *P* could cause the drug to be retained in the membrane longer, resulting the inhibition of drugs from being absorbed into the systemic circulation [14]. Besides, the existence of the human skin barrier (*stratum corneum*) is also one of the main challenges in developing transdermal formulation [15]. The barrier effect of the *stratum corneum* is most likely caused by its high density and low hydration [8]. Various strategies have been utilized to improve TDDSs, one of which is solid microneedles (SMNs).

SMNs are a transdermal permeation enhancement technique that comes from micrometer-sized needles. These needles are long enough to penetrate the stratum corneum but too short of stimulating pain receptors that are located in the dermis. SMNs have been used as a pre-treating step before applying the transdermal dosage form [16]. It is a potential and painless method to enhance the permeation of drugs by creating micropores into the skin. Thus, drugs could easily permeate across the barrier [9, 15]. The resulting micropores would close immediately after the SMNs are moved to prevent infection by pathogenic microorganisms [17].

Table 1. Valsartan transdermal gel formulation composition.

	%Composition (w/w)			
Compositions	F1	F2	F3	F4
Valsartan	1	1	1	1
Ethanol 95%	10	10	10	10
Carbopol 940	0.75	1	1.25	1.5
Triethanolamine	2.25	3	3.75	4.5
DMDM Hydantoin	0.1	0.1	0.1	0.1
Distilled water	ad 100	ad 100	ad 100	ad 100

To date, no studies have reported on combining SMN and transdermal gel for delivering VAL. Hence the present work was carried out to develop Carbopol-based VAL transdermal gel and SMN to improve its permeation through the skin.

2. Material and methods

2.1. Chemicals

VAL (purity: >98.0% T) (HPLC) was obtained from Tokyo Chemical Industry (Tokyo, Japan). Carbopol 940 and DMDM Hydantoin were purchased from Sigma-Aldrich Pte Ltd. (Singapore, Singapore). SMNs (Dermarollers®) were obtained from SQY® (Guangdong, China). Other materials were analytical grade

2.2. Preparation of transdermal gel

Various VAL transdermal gel was prepared using Carbopol as gel base [18]. Four different VAL transdermal gel formulations were prepared using various concentrations of Carbopol, as shown in Table 1. The gel was made by dispersing Carbopol in distilled water and then left for 24 h until it was completely hydrated. Triethanolamine (TEA) was added to the obtained dispersion, followed by homogenization at 1000 rpm for 15 min. After that, VAL was dissolved in 95% ethanol. The VAL solution and DMDM hydantoin were then added to the gel and homogenized at 1000 rpm for 15 min until homogenous.

2.3. pH measurement

pH measurement was conducted using a digital pH meter. The glass electrode was entirely soaked into the gel formulation at room temperature. This measurement was done in triplicate [19].

2.4. Viscosity study

The viscosity of gel was determined using Brookfield viscometer with suitable spindle speed and size [19]. In this study, the evaluation was performed at room temperature at 50 rpm using 50 g of sample, spindle number 7 and a total time of 60 s for one measurement.

2.5. Spreadability test

One of the ideal criteria required for the gel is it should possess good spreadability. The spreadability test of the gel was carried out by placing 0.5 g gel within a pre-recorded diameter of circle on a glass plate with a diameter of 25 cm. A second glass plate having the same dimension was placed over it. A weight of 500 g was allowed to rest on the upper glass plate for 5 min. The increase in diameter was measured and noted as spreadability (in cm) [20].

2.6. Extrudability test

Extrudability is an important parameter for evaluating gel formulation. Extrudability indicates the force that is required to remove the formulation from the tube. This test was done using the following method: The aluminum tube was filled with a known amount of formulation, and the tube was sealed by crimping both ends. The tube was placed between two glass slides. A weight of 500 g was applied to the top of the glass. The cap was removed, and the amount of the extruded gel was collected and noted. The extrudability of the formulation was calculated using the following equation [21]:

$$E = W/A$$

where E is extrudability, W is applied weight to extrude the formulation, and A is the area.

2.7. Gel strength determination

The gel strength was determined using the following method: a 100 ml borosilicate graduated measuring cylinder (diameter 1.5 in.) was filled with 60 g of the gel. A disc (diameter = 3 cm; thickness = 3 mm) mounted with 30 g of weight was placed above the gel surface. The time taken (in seconds) by the disc to sink 5 cm into the gel from the surface was measured as gel strength [22].

2.8. Drug content recovery

The drug content recovery was conducted by weighing 1 g of gel (containing 10 mg of VAL) and putting it in the 25 mL volumetric flask. The volume was then adjusted using ethanol 95%. The absorbance was measured triplicate using a validated UV-Vis Spectrophotometer at 231.4 nm. The determination of the concentration of VAL was performed by plotting the absorbance obtained to the calibration curve made from the standard solution of VAL in the concentration ranging from 0.5 to 32 µg/mL.

2.9. In vitro drug release evaluation

The *in vitro* release profile of VAL gel was measured using the membrane dialysis method [23, 24] (Figure 1A). Spectra-Por®, pore size of 12,000–14,000 MWCO dialysis membrane (Spectrum Medical Industries, CA, USA) was prepared and immersed

in PBS solution for 24 h. One gram of VAL gel was accurately weighed and placed in the dialysis membrane (25 × 50 mm) using spatula. The dialysis membrane was sealed and put into a 100 mL Duran bottle filled with PBS pH 7.4 and was placed on a magnetic stirrer. The temperature was maintained at 37 ± 1 °C. The rpm was set at 100 rpm during the evaluation. An aliquot of 1 ml was sampled at predetermined time intervals. The sampled solution was analyzed using a UV-Vis spectrophotometer at a wavelength of 231.4 nm. The result obtained was then calculated to determine the amount of drug released. The experiment was carried out in triplicates.

2.10. In vitro skin occlusivity evaluation

The occlusion properties of VAL gel were evaluated using the previously described method [25]. The test was carried out using Whatman filter paper (cut off 2.5 µm). 250 mg of the gel was applied to the Whatman filter paper and was placed on the top of a beaker filled with 50 mL of distilled water. The temperature was maintained at skin temperature (32 °C). Using a similar method, a beaker filled with 50 mL distilled water was covered with Whatman filter paper without gel working as the negative control. At predetermined time intervals (6, 24, 48 h), the systems were weighed to measure the water loss. The occlusivity (F_0) of the samples was determined using the following equation:

$$F_0 = \frac{W_0 - W_1}{W_0} \times 100\%$$

where W_0 is the water loss of the control system and W_1 is the water loss of the gel. No occlusion is indicated by zero value of F_0, and maximal occlusion is indicated by 100 values of F_0.

2.11. Ex vivo permeation study

The *ex vivo* permeation study was conducted using vertical Franz cell and abdominal skin from Wistar rats (Figure 1B). In order to obtain the skin, the rat's hair was removed using an electrical shaver and hair removal cream. Following this, the skins were collected after the rats were sacrificed. The full-thickness skins were collected by removing the fats attached to the skins. The skin was washed using PBS prior to the experiment. The diameters of the skins were 2.65 ± 0.18 mm. The skin collection was ethically permitted by the Health Ethical Committee at the Faculty of Medicine, Hasanuddin University, Indonesia. The skin was pre-treated using various lengths of SMNs (Dermaroller®), namely 0.5, 1.0, and 1.5 mm, creating 100 pores in the skin. The skin with a surface area of 4.9 cm^2 was placed between the donor and receptor compartment to facilitate the VAL permeation. The receptor compartment was filled with PBS pH 7.4. The temperature during the study was maintained at 37 ± 1 °C. Afterwards, 1 g of gel formulation (equal to 10 mg of VAL) was applied to the skin. At each predetermined time an aliquot of 1 mL was taken from the receptor compartment and then replaced by 1 mL of the fresh release medium to maintain the sink condition. All samples were analyzed by using UV-Vis spectrophotometry at a wavelength of 231.4 nm. The same method was used to compare abdominal skin without pre-treatment [26]. Additionally, the integrity of the skin following the application

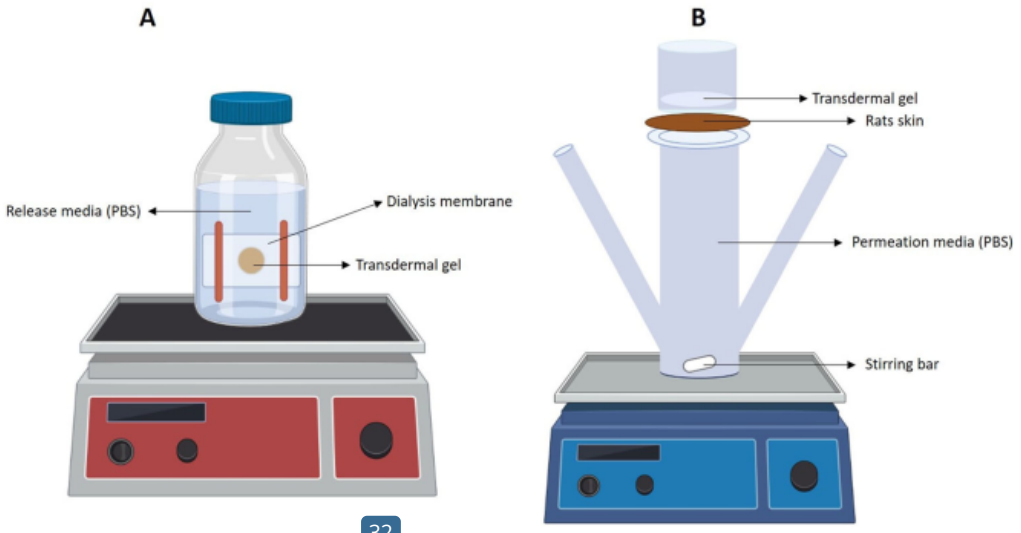

Figure 1. Schematic procedure of *in vitro* release study (A) and *ex vivo* permeation study (B) of VAL from transdermal gel.

of Dermaroller® was evaluated using Fourier transform infrared (FTIR) spectroscopy [27]. At the end of *ex vivo* permeation study, the skin was washed and analyzed using FTIR. Untreated skin sample was also analyzed as a control (Figure 1).

2.12. In vitro hemolysis

The safety and biocompatibility of VAL gel were determined from *in vitro* hemolytic activity study [28, 29]. This study was carried out using a fresh blood sample obtained from Wistar rats. Red blood cells (RBC) were separated from the plasma through centrifugation at 2000 rpm for 20 min. The RBC was washed three times using PBS, followed by vortex and centrifugation at 2000 rpm for 10 min. The washed RBC was resuspended in PBS to obtain a concentration of 10% (v/v). An aliquot of 100 µL of tested samples was added to 900 µL RBC and incubated at 37 °C for 1 h, followed by centrifugation at 7000 rpm for 10 min. Finally, the obtained supernatant was analyzed using UV-Vis Spectrophotometer at 540 nm. As a positive and negative control, blood samples were added with PBS and water, respectively. Calculation of the hemolysis percentage was done using the following equation:

$$\text{Hemolysis (\%)} = \frac{(\text{OD test sample}) - (\text{OD negative control}) \times 100}{(\text{OD positive control}) - (\text{OD negative control})}$$

3. Results and discussion

3.1. Preparation of VAL transdermal gel

This study was conducted as a proof of concept to develop a combination approach of SMNs and transdermal gel for VAL delivery. In this study, VAL was formulated

into the transdermal gel using Carbopol 940 as the polymer. Carbopol 940 is a hydrophilic polymer used in gel preparation. Carbopol would form acidic dispersion and undergo hydration when it was mixed with water. The addition of base is needed in order to obtain the viscous gel. To achieve this, TEA was added to neutralize the Carbopol dispersion [30]. A total of four VAL transdermal gel formulations were developed and evaluated to obtain the optimum formulation.

3.2. pH measurement

pH value is one of the important parameters that need to be considered. The pH of healthy skin is reported to be around 4.1–5.8 [31]. pH value plays an important role in maintaining skin barrier function. Acidic pH of the skin is responsible for controlling the presence of skin microflora [32, 33]. The barrier integrity of the skin was also affected by the pH value [34]. In this study, we used Carbomer as the main gelling agent. It has been reported by numerous studies that the gel formation prepared by Carbomer could occur effectively at neutral pH (around 7) [35, 36]. Therefore, the addition of TEA could neutralize the pH of the gels. The result showed that pH values of VAL transdermal gel were between 7.41 ± 0.01 and 7.56 ± 0.01 (Table 2). Although the obtained results were not in the range of the normal skin pH, a study conducted by Alberti et al. [37] stated that transdermal formulations with pH values of 4–10 are still well tolerated. In line with this study, a previous study showed that a pH value of 7 did not result in skin irritation [38]. Accordingly, the developed VAL transdermal gels were considered safe and could not possibly cause irritation to the skin.

3.3. Viscosity and spreadability study

The viscosity of VAL transdermal gel was measured and noted. The obtained results are depicted in Figure 2(A). The higher Carbopol concentration used in the formulation would result in higher viscosity. Dispersion and hydration of Carbopol in water result in acidic dispersion with low viscosity which a small portion of carboxyl groups present on the polymer chain dissociate. Neutralization using base would increase viscosity due to further dissociation of carboxyl group on the polymer and internal repulsion between polymer strands which causes uncoiling and expansion, resulting in swelling and gel formation [30, 39]. It was found that higher Carbopol concentration led to statistically different viscosity of the gel ($p < 0.05$). Additionally, it was also important to note that the pH of the formulations also increased with the increase of Carbomer and TEA concentration. As previously explained, the

Table 2. Result of pH, extrudability, gel strength, and drug content recovery test of VAL transdermal gel formulations (mean ± SD, $n = 3$).

Formula	pH	Extrudability (g/cm^2)	Gel strength (s)	Drug content recovery (%)
F1	7.41 ± 0.01	1.49 ± 0.18	36.20 ± 3.93	101.19 ± 0.13
F2	7.42 ± 0.01	1.45 ± 0.20	38.30 ± 4.09	102.67 ± 0.44
F3	7.50 ± 0	1.37 ± 0.17	39.88 ± 3.98	103.04 ± 0.56
F4	7.56 ± 0.01	1.34 ± 0.16	40.31 ± 4.58	103.41 ± 0.13

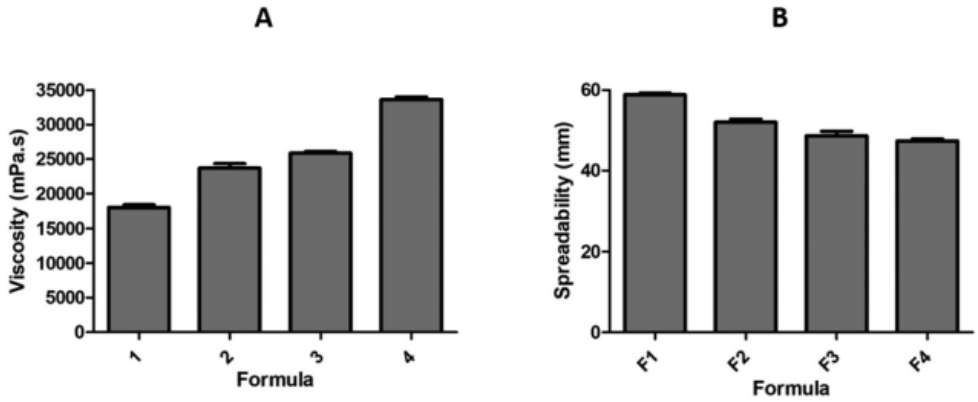

Figure 2. The result of (A) viscosity test and (B) spreadability test of VAL transdermal gel (mean ± SD, $n = 3$).

neutralization could affect the viscosity of the gels. The pH of F4 was found to be highest, followed by F3, F2 and F1. This could result in the higher viscosity of the formulation following the pH values of each formulation. VAL transdermal gels were then evaluated for their spreadability, as good spreadability is one of the ideal criteria for good gels. The spreadability of VAL transdermal gel showed in Figure 2(B). The spreadability could improve patient compliance and helps in the uniform application of gels. Spreadability value also affects the therapeutic efficacy of gel formulation [13, 20]. Higher spreadability value showed by VAL transdermal gel containing Carbopol with low concentration. This implies that viscosity and spreadability value were inversely related.

3.4. Extrudability test

Extrudability is an important parameter for evaluating gel formulation. This test indicates the force required to remove the formulation from the tube. The more gels extruded, the better extrudability since only lower energy was needed to extrude the gel from the aluminum tube. Extrudability values of VAL transdermal gel can be seen in Table 2. F1, which contains 0.75% Carbopol, exhibited the highest extrudability, while F4, containing 1.5% Carbopol, showed the lowest extrudability. Despite the difference, the extrudability values among VAL transdermal gels were statistically insignificant ($p > 0.05$). The result showed that VAL transdermal gel exhibited good extrudability [21, 40].

3.5. Gel strength determination

The result of gel strength determination is shown in Table 2. It plays a crucial role as low gel strength could lead to loss of gel integrity and fast gel removal, while high gel strength indicates very stiff gel. Discomfort when used by patients and difficulties in spreading the gel, are also caused by high gel strength. Optimal gel strength is characterized by a value of 25–50 s. All developed formulations showed gel strength values

that fall within the optimal range indicating VAL transdermal gel exhibits good gel strength. Furthermore, gel strength values were found to be not related to the Carbopol concentration used in the formulas as it did not statistically different ($p > 0.05$) [41, 42].

3.6. Drug content recovery

Drug content recovery test is carried out to determine the amount of VAL in the final product. The result in Table 2 showed drug content in the VAL transdermal gels was between 101.19 and 103.03%, which implies the method used in gel fabrication produced a homogeneous formulation. Moreover, it confirms that the fabrication method did not affect the amount of VAL in the formulation. The results obtained also were fall within the requirement of drug content recovery set by the International Council for Harmonization (ICH), which was in the range of 95–105%. [43].

3.7. In vitro drug release evaluation

The *in vitro* drug releases of VAL transdermal gels are depicted in Figure 3(A). Specifically, the data showed that 10.78 ± 0.46, 9.64 ± 0.35, 9.08 ± 0.43, and 8.44 ± 0.25 mg of VAL were released from F1, F2, F3, and F4, respectively, after 8 h. Specifically, it was found that in the first 2 h, all formulations exhibited burst release,

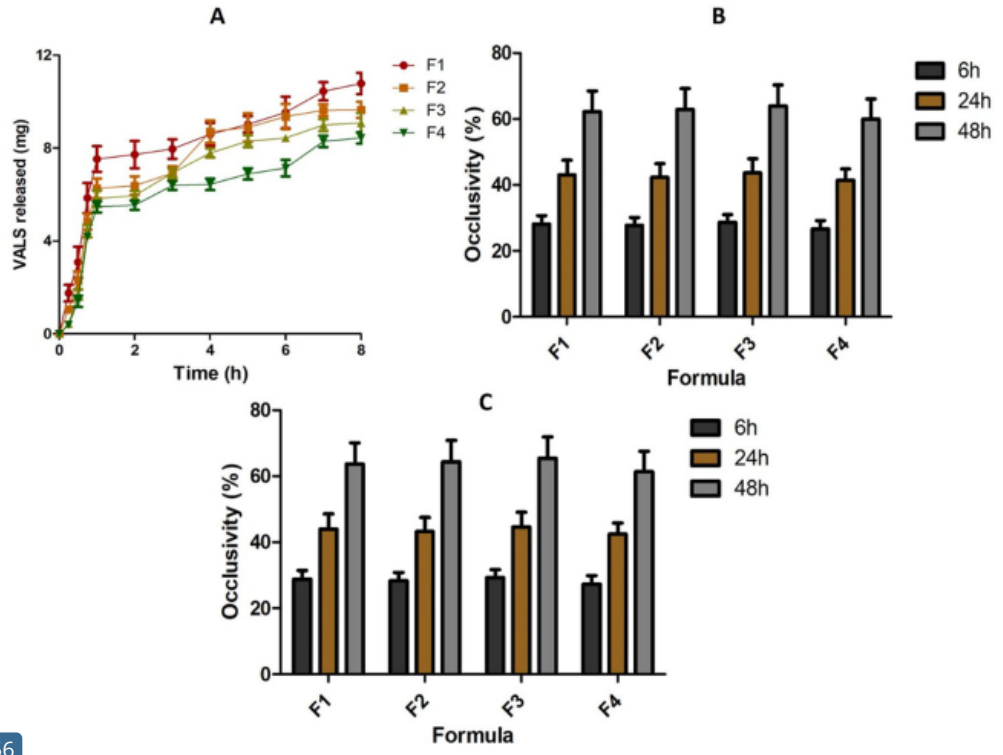

Figure 3. (A) *In vitro* release profile, (B) *in vitro* occlusivity of VALS transdermal gel and *in vitro* occlusivity of blank transdermal gel (C) (mean ± SD, $n = 3$).

showing the release percentage of around 80%. Afterwards, the sustained release manner was shown in the following hours. The burst release occurred possibly due to the presence of VAL on the outer surface of the gel or in the gel surface layers voids. This phenomenon was also reported previously [44]. Analyzed statistically, the VAL released from gel formulation were significantly different ($p < 0.05$), indicating that Carbopol concentration affected the release of VAL. A higher amount of VAL released was observed as the concentration of Carbopol decreased in the formulation. This finding was in line with a previous study [45]. This was because increasing Carbopol concentration would form high viscosity of the polymeric system, as the carboxyl groups dissociate, leading to electrostatic repulsion, resulting in the tight and hard gel. The formed gel would have a more rigid structure. This would hinder the diffusion of drug from the polymer matrix and decrease the amount of VAL released [46, 47].

3.8. *In vitro* skin occlusivity evaluation

This test was performed to evaluate the ability of VAL transdermal gel formulation to maintain the hydration characteristic of the skin. It indicates the prevention of water loss by the formulations. The results are presented in Figure 3(B). All formulations showed high occlusivity. The occlusivity of formulations would affect the amount of drugs in the skin. Higher occlusivity could increase skin hydration which facilitates drug penetration. This is due to the reduction of corneocyte gaps [48, 49]. Additionally, it was also observed that there was no significant difference ($p > 0.05$) in the occlusivity values between all formulations with the control formulations, as shown Figure 3(C). Accordingly, the addition of VAL did not alter the occlusivity of Carbomer-based gels. Several studies have shown the benefits of the occlusivity of topical preparation in the transdermal delivery system. The occlusivity of the preparations did not cause damage and irritation to the skin [50–52]. Importantly, the values obtained in our study were found to be comparable with several previous reports. Accordingly, it might be hypothesized that the occlusivity properties of the gel did not possibly cause any damage in the skin.

3.9. *Ex vivo* permeation study

To evaluate the permeation of VAL from transdermal gel, an *ex vivo* permeation study was carried out. This study was performed using abdominal skin from Wistar rats. The skin was pre-treated using Dermaroller® (SMN) with various needle lengths, namely 0.5, 1, and 1.5 mm. The illustration of the administration of Dermarollers® and the pores created in the skin are shown in Figure 4. The permeation profile of VAL transdermal gel is illustrated in Figure 5. All formulations exhibited higher permeation when it was pre-treated using Dermaroller® compared to permeation from non-treated abdominal skin ($p < 0.05$). The mechanism behind it was "poke and patch." Micropores were formed when Dermaroller® was applied to the skin surface as the microneedle penetrated the skin barrier (*stratum corneum*). Thus, when the transdermal gel was applied, the drug could easily pass the barrier and penetrate into

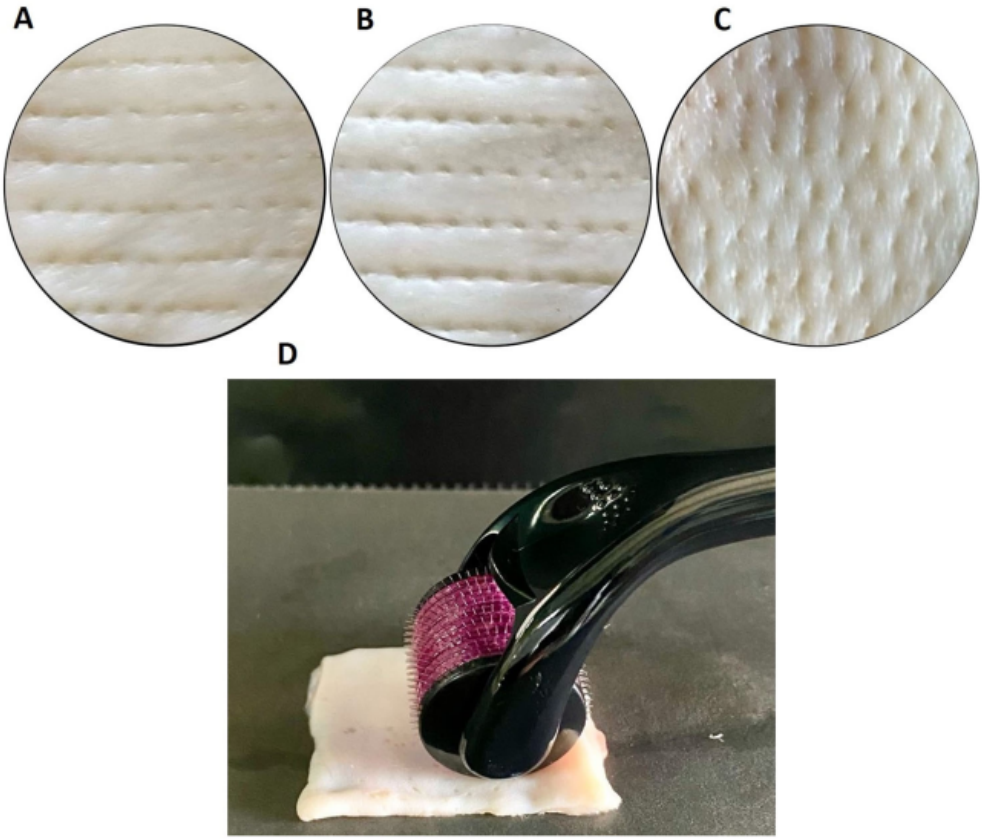

Figure 4. The representative images of the administration of Dermarollers® (A) and the pores created in the skin followong the administration of Dermarollers® with lenghts of 0.5 mm (B), 1 mm (C) and 1.5 mm (D).

the skin [15, 53]. Furthermore, the various microneedle lengths also affected the drug permeation profile in all formulations. It was clearly observed that the longer length of microneedle exhibits a higher permeation profile of VALS due to deeper penetration of the drug [54].

Without the use of MNs, the percentages of permeation of VALS were found to be $5.44 \pm 0.01\%$, $498 \pm 0.02\%$, $4.61 \pm 0.01\%$, and $4.49 \pm 0.02\%$ of VALS permeated from F1, F2, F3, and F4, respectively. As shown in Figure 3, pre-treated with Dermaroller® 0.5 mm was able to enhance the percentages of permeation to $14.33 \pm 0.04\%$ for F1, $13.92 \pm 0.07\%$ for F2, $12.05 \pm 0.01\%$ for F3, and $10.63 \pm 0.09\%$ for F4. Furthermore, the permeation percentages were significantly improved ($p < 0.05$) after the use of Dermarollers® with lengths of 1 mm, and 1.5 mm, respectively. The results showed that $15.37 \pm 0.08\%$, $14.96 \pm 0.08\%$, $12.44 \pm 0.04\%$, and $11.06 \pm 0.17\%$ of VAL permeated from transdermal gels F1, F2, F3, and F4, respectively after the administration of 1 mm Dermaroller®. Finally, the use of 1.5 mm Dermarolles® increased the permeation percentages up to $16.92 \pm 0.04\%$ for F1 $15.68 \pm 0.09\%$ for F2, $14.77 \pm 0.02\%$ for F2 and $12.97 \pm 0.15\%$ for F3. Analyzed statistically, there was a significant different ($p < 0.05$) on drug permeation against various length of microneedle. In line with the *in vitro* release study, the increase of Carbopol concentration could decrease the

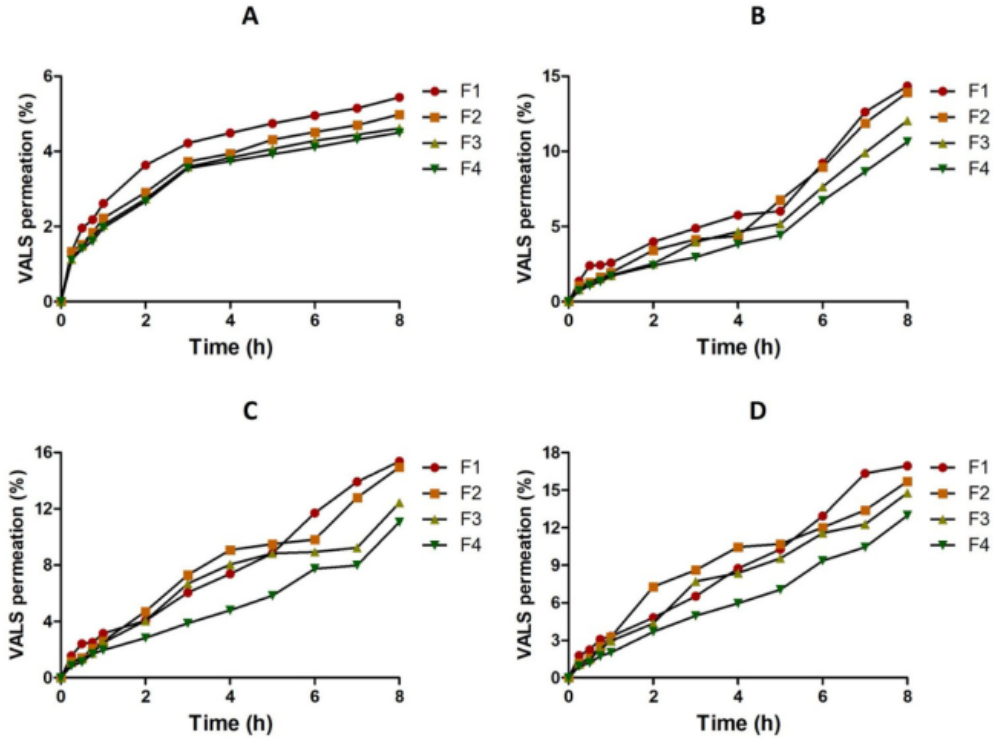

Figure 5. *Ex vivo* permeation profile of VALS transdermal gel (A)without MNs, (B) with MNs 0.5 mm, (C) with MNs 1 mm, and (D) with MNs 1.5 mm (mean ± SD, $n = 3$).

permeation of VAL from the formulation due to the high viscosity of the polymeric system as a result of the carboxyl groups dissociating and electrostatic repulsion, producing a tight gel structure [46, 47]. Therefore, F1 was considered as the optimum formula. Furthermore, the results showed that the permeation coefficient values of VALS permeated from F1 were observed to be 0.032 ± 0.002 cm/h for untreated skin, 0.047 ± 0.002 cm/h for the application of 0.5 mm Dermaroller®, 0.059 ± 0.003 cm/h for the application of 1 mm Dermaroller® and 0.065 ± 0.03 cm/h for the application of 1.5 mm Dermaroller®. As the permeation coefficient value increased with the increase of length needle, F1 combined with Dermaroller® 1.5 mm was chosen as the optimum treatment condition for VAL permeation. Several studies have previously reported that microneedles with a length of around 1.5 mm did not cause any discomfort when it was used by the patient [55–57].

Following the integrity evaluation using FTIR (Figure 6), it was found that the untreated skin showed noticeable peaks at 2902 and 2756 cm^{-1} due to asymmetric hydrocarbon stretching and symmetric CH_2 stretching, respectively. The presence of a hydrocarbon area indicates the ceramide and the fatty acid contained in the *stratum corneum*. Moreover, other peaks were also observed at 1678 and 1518 cm^{-1} due to the presence of the amide I and amide II bonds, respectively, in the corneocytes' keratin [27]. Importantly, all these peaks were also observed in all treated skins with negligible changes in intensity. Accordingly, the administration of Dermarollers® did not change the integrity of the skin.

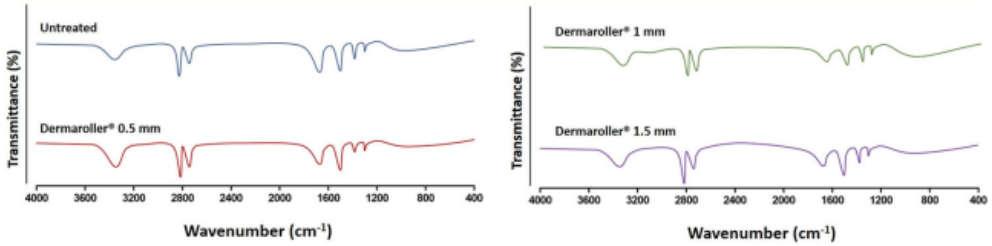

Figure 6. FTIR spectrum of skin indicating the integrity following the administration of Dermaroller®.

Table 3. Hemolysis percentage of VALS transdermal gel (mean ± SD, $n = 3$).

Hemolysis (%)				
Concentration (µg/mL)	F1	F2	F3	F4
500	2.97 ± 0.28	3.05 ± 0.30	3.08 ± 0.32	3.16 ± 0.34
50	2.23 ± 0.30	2.20 ± 0.21	2.03 ± 0.20	2.22 ± 0.28
5	0.98 ± 0.11	1.14 ± 0.12	1.05 ± 0.11	1.17 ± 0.14

3.10. *In vitro* hemolysis

This test was carried out to determine the safety, biocompatibility, and initial toxicity of the developed formulation against erythrocytes. In this study, we evaluated the hemolysis ability of VAL from F1 as the optimum formulation. Hemolysis percentage values were showed in Table 3. All formulations had hemolysis percentage values between 0.98 and 3.19%. Hemolysis percentage values were previously reported to be safe when less than 5%. The result clearly indicates that VALS transdermal gel would be safe to use at the tested concentration [58, 59].

The overall outcomes resulting from this investigation have proven the potential ability of SMNs to assist the transdermal delivery of VALS from polymeric hydrogel to avoid the drawbacks of oral delivery. Our study suggested that the permeation of VALS from conventional transdermal hydrogel was significantly lower when compared to its combination with SMNs with no toxicity possibility. To show the efficacy of this combination, further *in vivo* studies should be considered to assess the pharmacokinetic, pharmacodynamic and skin irritation studies.

4. Conclusion

The present study focused on the development of Carbopol-based VALS transdermal gel and combination with microneedles. The developed formulations were found to produce gels with good physical characteristics. Furthermore, a combination with a microneedle (Dermaroller®) showed improved permeation of VALS into the skin significantly. Microneedles with a length of 1.5 mm exhibited the highest permeation compared to other lengths. Importantly, *in vitro* hemolysis study showed hemolysis percentage below 5%, indicating that VAL transdermal gels were considerably safe to use. This study successfully developed a new approach for VALS drug delivery to treat hypertension in the future. However, further studies are required to investigate

the effectiveness of this approach, including *in vivo* pharmacokinetics and toxicity using suitable animal models.

Disclosure statement

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References

[1] Oparil S, Acelajado MC, Bakris GL, et al. Hypertension. Nat Rev Dis Prim. 2019;4:139–148.
[2] Bazzano LA, Pogribna U, Whelton PK. Hypertension. Int Encycl Public Heal. 2016;4:123–133.
[3] Singh S, Shankar R, Singh GP. Prevalence and associated risk factors of hypertension: a cross-sectional study in urban varanasi. Int J Hypertens. 2017;2017:5491838.
[4] Forouzanfar MH, Afshin A, Alexander LT, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the global burden of disease study 2015. Lancet. 2016;388(10053):1659–1724.
[5] Nixon RM, Müller E, Lowy A, et al. Valsartan vs. other angiotensin II receptor blockers in the treatment of hypertension: a meta-analytical approach. Int J Clin Pract. 2009;63(5):766–775.
[6] Bhosale SS, Avachat AM. Design and development of ethosomal transdermal drug delivery system of valsartan with preclinical assessment in wistar albino rats. J Liposome Res. 2013;23(2):119–125.
[7] Ahad A, Al-Mohizea AM, Al-Jenoobi FI, et al. Transdermal delivery of angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs) and others for management of hypertension. Drug Deliv. 2016;23(2):579–590.
[8] Alkilani AZ, McCrudden MTC, Donnelly RF. Transdermal drug delivery: innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum. Pharmaceutics. 2015;7(4):438–470.
[9] Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol. 2008;26(11):1261–1268.
[10] Suryakumari C, Narender M, Umasankar K, et al. Formulation and evaluation of tacrolimus transdermal gel. J. Drug Delivery Ther. 2019;9(6-s):110–118.
[11] Patel J, Patel B, Banwait H, et al. Formulation and evaluation of topical diclofenac sodium gel using different gelling agent. Int Jaurnal Drug Dev Res. 2011;3:156–164.
[12] Iqbal B, Ali J, Baboota S. Recent advances and development in epidermal and dermal drug deposition enhancement technology. Int J Dermatol. 2018;57(6):646–660.
[13] Ahad A, Aqil M, Ali A. Investigation of antihypertensive activity of carbopol valsartan transdermal gel containing 1,8-cineole. Int J Biol Macromol. 2014;64:144–149.
[14] Liu X, Testa B, Fahr A. Lipophilicity and its relationship with passive drug permeation. Pharm Res. 2011;28(5):962–977.

[15] Jung JH, Jin SG. Microneedle for transdermal drug delivery: current trends and fabrication. J Pharm Investig. 2021;51(5):503–517.
[16] Waghule T, Singhvi G, Dubey SK, et al. Microneedles: a smart approach and increasing potential for transdermal drug delivery system. Biomed Pharmacother. 2019;109:1249–1258.
[17] Ita K. Transdermal delivery of drugs with microneedles: strategies and outcomes. J Drug Deliv Sci Technol. 2015;29:16–23.
[18] Enggi CK, Isa HT, Sulistiawati S, et al. Development of thermosensitive and mucoadhesive gels of cabotegravir for enhanced permeation and retention profiles in vaginal tissue: a proof of concept study. Int J Pharm. 2021;609:121182.
[19] Aiyalu R, Govindarjan A, Ramasamy A. Formulation and evaluation of topical herbal gel for the treatment of arthritis in animal model. Brazilian J Pharm Sci. 2016;52:493–507.
[20] Ahad A, Aqil M, Kohli K, et al. Design, formulation and optimization of valsartan transdermal gel containing iso-eucalyptol as novel permeation enhancer: preclinical assessment of pharmacokinetics in Wistar albino rats. Expert Opin Drug Deliv. 2014;11(8):1149–1162.
[21] Dudhipala N, Gorre T. Neuroprotective effect of ropinirole lipid nanoparticles enriched hydrogel for Parkinson's disease: in vitro, ex vivo, pharmacokinetic and pharmacodynamic evaluation. Pharmaceutics. 2020;12(5):448–424.
[22] Algahtani MS, Ahmad MZ, Ahmad J. Nanoemulsion loaded polymeric hydrogel for topical delivery of curcumin in psoriasis. J Drug Deliv Sci Technol. 2020;59:101847.
[23] Permana AD, McCrudden MTC, Donnelly RF. Enhanced intradermal delivery of nanosuspensions of antifilariasis drugs using dissolving microneedles: a proof of concept study. Pharmaceutics. 2019;11(7):346.
[24] Permana AD, Paredes AJ, Volpe-Zanutto F, et al. Dissolving microneedle-mediated dermal delivery of itraconazole nanocrystals for improved treatment of cutaneous candidiasis. Eur J Pharm Biopharm. 2020;154:50–61.
[25] Malik DS, Kaur G. Nanostructured gel for topical delivery of azelaic acid: designing, characterization, and in-vitro evaluation. J Drug Deliv Sci Technol. 2018;47:123–136.
[26] Ahmed KS, Shan X, Mao J, et al. Dermaroller® microneedles-mediated transdermal delivery of doxorubicin and celecoxib co-loaded liposomes for enhancing the anticancer effect. Mater Sci Eng C Mater Biol Appl. 2019;99:1448–1458.
[27] Talib S, Ahmed N, Khan D, et al. Chitosan-chondroitin based artemether loaded nanoparticles for transdermal drug delivery system. J Drug Deliv Sci Technol. 2021;61:102281.
[28] Ananda PWR, Elim D, Zaman HS, et al. Combination of transdermal patches and solid microneedles for improved transdermal delivery of primaquine. Int J Pharm. 2021;609:121204.
[29] Qonita HA, Syafika N, Valensie V, et al. Development water in oil nanoemulsion of diethylcarbamazine for enhanced the characteristics for lymphatic targeting: a proof of concept study. J Indian Chem Soc. 2022;99(4):100395.
[30] Barry BW, Meyer MC. The rheological properties of carbopol gels I. Continuous shear and creep properties of carbopol gels. Int J Pharm. 1979;2(1):1–25.
[31] Proksch E. pH in nature, humans and skin. J Dermatol. 2018;45(9):1044–1052.
[32] Paudel KS, Milewski M, Swadley CL, et al. Challenges and opportunities in dermal/transdermal delivery. Ther Deliv. 2010;1(1):109–131.
[33] Lambers H, Piessens S, Bloem A, et al. Natural skin surface pH is on average below 5, which is beneficial for its resident flora. Int J Cosmet Sci. 2006;28(5):359–370.
[34] Gorzelanny C, Mess C, Schneider SW, et al. Skin barriers in dermal drug delivery: which barriers have to be overcome and how can we measure them? Pharmaceutics. 2020;12(7):684–631.

[35] Tripathi P, Kumar A, Jain PK, et al. Carbomer gel bearing methotrexate loaded lipid nanocontainers shows improved topical delivery intended for effective management of psoriasis. Int J Biol Macromol. 2018;120(Pt A):1322–1334.
[36] Zhang Y, Ng W, Hu J, et al. Formulation and in vitro stability evaluation of ethosomal carbomer hydrogel for transdermal vaccine delivery. Colloids Surf B Biointerfaces. 2018;163:184–191.
[37] Alberti I, Grenier A, Kraus H, et al. Pharmaceutical development and clinical effectiveness of a novel gel technology for transdermal drug delivery. Expert Opin Drug Deliv. 2005;2(5):935–950.
[38] Al-Suwayeh SA, Taha EI, Al-Qahtani FM, et al. Evaluation of skin permeation and analgesic activity effects of carbopol lornoxicam topical gels containing penetration enhancer. Sci World J. 2014;2014:1–9.
[39] Mastropietro D, Park K, Omidian H. Polymers in oral drug delivery. In: Ducheyne P, editor. Comprehensive biomaterials II. Oxford: Elsevier; 2017. p. 430–444.
[40] Gupta R, Gupta GD. Formulation development and evaluation of anti-inflammatory potential of cordia obliqua topical gel on animal model. Pharmacogn J. 2017;9(6s): s93–s98.
[41] Mahajan HS, Gattani S. In situ gels of metoclopramide hydrochloride for intranasal delivery: in vitro evaluation and in vivo pharmacokinetic study in rabbits. Drug Deliv. 2010;17(1):19–27.
[42] Morsi N, Ibrahim M, Refai H, et al. Nanoemulsion-based electrolyte triggered in situ gel for ocular delivery of acetazolamide. Eur J Pharm Sci. 2017;104:302–314.
[43] Walfish S. A statistical perspective on the ICH Q2A and Q2B guidelines for validation of analytical methods. BioPharm Int. 2006;19:28–36.
[44] Khan S, Minhas MU, Tekko IA, et al. Evaluation of microneedles-assisted in situ depot forming poloxamer gels for sustained transdermal drug delivery. Drug Deliv Transl Res. 2019;9(4):764–782.
[45] Li S, Lin S, Daggy BP, et al. Effect of HPMC and Carbopol on the release and floating properties of gastric floating drug delivery system using factorial design. Int J Pharm. 2003;253(1–2):13–22.
[46] Suhail M, Wu PC, Minhas MU. Using carbomer-based hydrogels for control the release rate of diclofenac sodium: preparation and in vitro evaluation. Pharmaceuticals. 2020; 13(11):399–317.
[47] Nakanishi T, Kaiho F, Hayashi M. Improvement of drug release rate from carbopol 934P formulation. Chem Pharm Bull. 1998;46(1):171–173.
[48] Ammar HO, Ghorab MM, Mostafa DM, et al. Folic acid loaded lipid nanocarriers with promoted skin antiaging and antioxidant efficacy. J Drug Deliv Sci Technol. 2016;31: 72–82.
[49] Permana AD, Utami RN, Courtenay AJ, et al. Phytosomal nanocarriers as platforms for improved delivery of natural antioxidant and photoprotective compounds in propolis: an approach for enhanced both dissolution behaviour in biorelevant media and skin retention profiles. J Photochem Photobiol B. 2020;205:111846.
[50] Shrotriya S, Ranpise N, Satpute P, et al. Skin targeting of curcumin solid lipid nanoparticles-engrossed topical gel for the treatment of pigmentation and irritant contact dermatitis. Artif Cells Nanomed Biotechnol. 2018;46(7):1471–1482.
[51] Shrotriya SN, Ranpise NS, Vidhate BV. Skin targeting of resveratrol utilizing solid lipid nanoparticle-engrossed gel for chemically induced irritant contact dermatitis. Drug Deliv Transl Res. 2017;7(1):37–52.
[52] Wavikar P, Vavia P. Nanolipidgel for enhanced skin deposition and improved antifungal activity. AAPS PharmSciTech. 2013;14(1):222–233.
[53] Avcil M, Çelik A. Microneedles in drug delivery: progress and challenges. Micromachines. 2021;12(11):1321–1315.
[54] Tobin KV, Fiegel J, Brogden NK. Thermosensitive gels used to improve microneedle-assisted transdermal delivery of naltrexone. Polymers. 2021;13(6):933–915.

[55] Kim YC, Park JH, Prausnitz MR. Microneedles for drug and vaccine delivery. Adv Drug Deliv Rev. 2012;64(14):1547–1568.
[56] Chu S, Foulad DP, Mesinkovska NA. Safety profile for microneedling: a systematic review. Dermatol Surg. 2021;47(9):1249–1254.
[57] Salloum A, Bazzi N, Maalouf D, et al. Microneedling in vitiligo: a systematic review. Dermatol Ther. 2020;33:1–7.
[58] Greco I, Molchanova N, Holmedal E, et al. Correlation between hemolytic activity, cytotoxicity and systemic in vivo toxicity of synthetic antimicrobial peptides. Sci Rep. 2020;10(1):1–13.
[59] Zhou HY, Zhang YP, Zhang WF, et al. Biocompatibility and characteristics of injectable chitosan-based thermosensitive hydrogel for drug delivery. Carbohydr Polym. 2011; 83(4):1643–1651.

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Publication

---

58 Franklin Chimaobi Kenechukwu, Anthony Amaechi Attama, Emmanuel Chinedum Ibezim. "Novel solidified reverse micellar solution-based mucoadhesive nano lipid gels encapsulating miconazole nitrate-loaded nanoparticles for improved treatment of oropharyngeal candidiasis", Journal of Microencapsulation, 2017 <1 %
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---

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---

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---

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---

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---

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---

64 Lather, Viney, Dharmpal Sharma, and Deepti Pandita. "Proniosomal gel-mediated transdermal delivery of bromocriptine: in vitro and ex vivo evaluation", Journal of Experimental Nanoscience, 2016. <1 %
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---

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---

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---

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---

68 Shilpa Shrotriya, Nisharani Ranpise, Pournima Satpute, Bhagvat Vidhate. "Skin targeting of curcumin solid lipid nanoparticles-engrossed topical gel for the treatment of pigmentation and irritant contact dermatitis", Artificial Cells, Nanomedicine, and Biotechnology, 2017
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---

70 Mengyang Liu, Manisha Sharma, Guo-Liang Lu, Naibo Yin, Murad Al Gailani, Sree Sreebhavan, Jingyuan Wen. " Preformulation studies of -glutathione: physicochemical properties, degradation kinetics, and cytotoxicity investigations ", Drug Development and Industrial Pharmacy, 2020 <1 %
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---

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---

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