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Combinatorial Approach of Polymeric Patches and Solid Microneedles for Improved Transdermal Delivery of Valsartan: A Proof-of-Concept Study

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Abstract: Valsartan (VALS) is a first-line therapy for hypertension that belong to the Angiotensin II Receptor Blockers class. VALS is currently administered orally, but it is associated with its low bioavailability. The transdermal route can be an alternative to overcome this problem. However, this route has low permeation caused by the presence of *stratum corneum* on the skin. The use of permeation enhancers is needed. This study aims to determine the effect of PEG 400 concentration on physical characteristics and release of VALS from transdermal patch preparations and determine the effect of solid microneedles on VALS permeation. The transdermal patch formula was made using HPMC as a base and PEG 400 as a permeation enhancer with various concentrations. The patches were evaluated for their physical appearance, weight uniformity, thickness, moisture content, folding endurance, drug content, *in vitro* drug release, *in vitro* drug permeation, and *ex vivo* permeation test. The results showed that all formulations showed good characteristics for transdermal administration, and the use of PEG 400 could increase the permeation of VALS. Importantly, when combined with solid microneedles, the permeation of VALS was significantly improved. To conclude, the combination of VALS patch transdermal and MNs can increase the amount of VALS permeated.

Keywords: valsartan; transdermal patch; solid microneedle; permeation profiles.

1. Introduction

Hypertension is defined as an increase in blood pressure (BP) exceeding ≥140 mmHg systolic and 90 mmHg diastolic, which causes pathological changes in blood vessels and is a major cause of stroke and cardiovascular disease (CV), and other diseases [1, 2]. Hypertension continues to increase globally every year, with 1.39 billion people (31.1% of the world's total adult population [3]. In addition, hypertension (pre-hypertension and other dangerous high blood pressure) is known to cause the death of 8.5 million people, also estimated to increase to 1.56 billion in 2025 [2, 4].

One of the drugs that can be used to treat hypertension is valsartan (VALS) (Fig. 1). Valsartan is a specific angiotensin II receptor blocker (ARB) acting on the AT1 receptor subtype. VALS is currently used orally with low bioavailability of about 25% (due to the first-pass effect), a mean biological half-life of 7.5 hours, poorly absorbed from the gastrointestinal

tract and has a maximum plasma concentration of 2-4 hours which can be reduced by food intake leads to decrease its pharmacological effect. Also, there is no report about skin irritation towards VALS [3, 5]. To overcome this problem, transdermal administration can be a promising alternative.

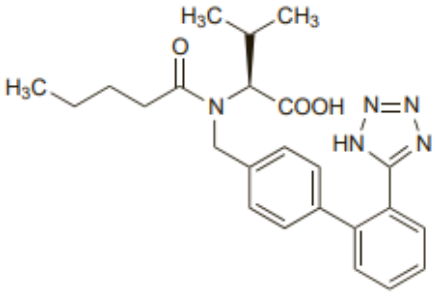

Figure 1. Chemical structure of valsartan.

The transdermal drug delivery system (TDDS) provides many advantages, such as bypassing the first-pass effect, no interference with gastrointestinal fluid, painless, and enhanced patient compliance [6, 7]. One transdermal dosage form is the patches polymer matrix. The patch is known to be the most convenient dosage form in terms of productivity, production costs, and practical use [8, 9]. The polymer matrix transdermal patch can be formulated using a polymer such as Hydroxypropyl Methylcellulose (HPMC) [10, 11]. HPMC is a semi-synthetic, biocompatible, and viscoelastic polymer used as an additive and controlled delivery component in transdermal drug delivery systems [12, 13].

Even though TDDS offers many advantages, this administration has drawbacks, such as low permeability because of the stratum corneum of the skin [7, 14]. In addition, a drug can be delivered transdermally if it has a molecular weight (<500 Dalton), log P (1-3), and melting point (< 200°C) [15]. Meanwhile, VALS has a molecular weight (435,5 Dalton), log partition coefficient (4,5), and melting point (116-117ºC) [5]. Thus, valsartan does not meet all the requirements for good transdermal drug delivery.

To increase the permeation of drug molecules or drug delivery via the transdermal route, permeation enhancer agents can be used [12, 16]. Polyethylene glycol (PEG) 400 is a permeation enhancer agent generally used in transdermal patch preparations [17]. According to previous research [18], in HPMC-based transdermal preparations, PEG 400 can increase the permeation of drug molecules through the skin. The greater the amount of PEG used, the greater the drug released [19]. In addition, solid microneedles can be added to increase the permeation of drug molecules further. Solid microneedles (MNs) are micron-sized components (100-1000 µm) made of materials such as stainless steel or hard polymers. When applied to the skin, MNs create hydrophilic micropores that can penetrate the stratum corneum but avoid contact with the nerve endings in the dermis layer. Topical drugs, such as patch preparations, can be absorbed systemically through these micropores, thereby increasing the therapeutic effect. The time the drug can absorb through the skin depends on how long the micropores remain open on the skin's surface. Based on the natural healing process of human and animal skin, micropores can close for up to 48 hours [7, 20–22].

This study aimed to determine the effect of PEG 400 concentration on physical characteristics and release of VALS from transdermal patch preparations and determine the effect of solid microneedles on VALS permeation.

2. Materials and Methods

2.1. Materials.

Valsartan (purity of 98%), (Poly(ethylene glycol) (PEG) 400, and hydroxypropyl methylcellulose (HPMC) were purchased from Sigma-Aldrich Pte Ltd. (Singapore, Singapore). Solid microneedles (Dermarollers®) were obtained from SQY® (Guangdong, China).

2.2. Design of formulation.

Transdermal patches were prepared by weighing the composition accurately, as shown in Table 1. Initially, HPMC K-100 was dissolved in warm distilled water and stirred using a homogenizer for 10 minutes. Afterward, PEG 400 and glycerin were added to the polymer solution, then stirred again until homogeneous using a homogenizer (Solution 1). Dissolved VALS has been weighed carefully in 96% ethanol and mixed with solution 1. The mixture was stirred using a homogenizer for 15 minutes and poured into a petri dish for as much as 15 grams. Finally, the formulations were kept in a desiccator until the patch dried [23].

Table 1. Design of VALS transdermal patch formulation.

Ingredients %(w/w)	**F1**	**F2**	**F3**
Valsartan	2	2	2
Ethanol 96%	47.5	47.25	47
HPMC	2	2	2
Glycerin	0.5	0.5	0.5
PEG 400	0.5	1	1.5
Distilled water	Ad 100	Ad 100	Ad 100

2.3. Characterization of VALS transdermal patches.

2.3.1. Weight and thickness uniformity.

The weight uniformity of patches was conducted by weighing each formula in triplicate then the average weight and standard deviation were calculated. The thickness of patches was carried out by using calibrated digital calipers and measured at 4 different points. The average thickness, standard deviation, and relative standard deviation (RSD) were calculated [23, 24].

2.3.2. Moisture content.

The moisture content of the VALS transdermal patch was determined by using a moisture analyzer, and the test was performed in triplicate.

2.3.3. Folding endurance.

A folding endurance test was performed by folding the patch repeatedly at the same spot until it broke. The number of folds made without breaking is considered the value of the fold resistance [25, 26].

2.3.4. Drug content.

VALS transdermal patch equivalent to 10 mg of VALS was weighed and dissolved in 10 mL 96% ethanol. The solution was diluted to 10 parts per million, and the absorbance of the solution was measured at the maximum wavelength (230.2 nm) using a UV-Vis

spectrophotometer. Furthermore, the drug content was calculated against the absorbance of the standard curve [20].

2.4. In vitro release study.

In vitro release of VALS transdermal patch was carried out by membrane dissolution model. A transdermal patch equivalent to 10 mg of VALS was inserted into the dialysis membrane. The dialysis membrane filled with the patch was immersed in a sealed bottle containing 100 mL of phosphate buffer saline (PBS) pH 7.4, then stirred constantly using a shaker at 37°C at 100 rpm. The release medium was collected (1 mL) at the pre-determined time interval (15, 30, 45, 60, 120, 180, 240, 300, 360, 420, and 480 minutes) and replaced with fresh medium at the same temperature and volume. The sample's absorbance was measured using a UV-Vis spectrophotometer at the maximum wavelength (321.4 nm), and the concentration of the drug was calculated against the standard curve [27].

2.5. In vitro permeation study.

In vitro permeation studies were carried out using Franz diffusion cells and synthetic cellophane membranes. The receptor compartment of the apparatus was filled with 10 mL of PBS pH 7.4 solution, and a magnetic bead was inserted for stirring purposes. The cellophane membrane was immersed in PBS pH 7.4 solution before it was attached to the Franz diffusion cell compartment receptor. Furthermore, a transdermal patch equivalent to 10 mg of VALS was placed between the donor and receptor compartment. The diffusion cell was placed on a magnetic stirrer and agitated at 100 rpm with a maintained temperature (±37°C). Sample (1 mL) were then withdrawn at the pre-determined time interval (15, 30, 45, 60, 120, 180, 240, 300, 360, 420, and 480 minutes). An equal medium immediately replaced each sample taken with the same temperature. The sample obtained was diluted to obtain an absorption value adjusted with the standard curve range, then the absorption was measured at the maximum wavelength using a UV-Vis spectrophotometer [28, 29].

2.6. Ex vivo permeation study.

Ex vivo permeation studies were performed using Franz diffusion cell, as previously described, but using the abdominal skin of a Female Sprague-Dawley rat as the biological membrane. The skin sample was shaved and washed with PBS pH 7.4 before the test. The receptor compartment of the apparatus was filled with 10 mL of PBS pH 7.4 solution, and a magnetic bead was inserted for stirring purposes. To investigate the effect of MNs on VALS permeation, the skin sample was pretreated with dermaroller® (containing MNs) before it was placed with a transdermal patch equivalent to 10 mg of VALS between the donor and receptor compartment. The assembly was placed on a magnetic stirrer with a maintained temperature (±37°C) and stirring rate of 100 ppm. Sample (1 mL) were then withdrawn at the pre-determined time interval (15, 30, 45, 60, 120, 180, 240, 300, 360, 420, and 480 minutes). An equal medium immediately replaced each sample taken with the same temperature. The sample obtained was diluted to obtain an absorption value adjusted with the standard curve range, then the absorption was measured at the maximum wavelength using a UV-Vis spectrophotometer [6, 28].

2.7. Statistical analysis.

Data obtained from all the tests were calculated using Microsoft® Excel® 2016 (Microsoft Corporation, Redmond, USA) for means ± standard deviation (SD). The statistical analysis was performed using GraphPad Prism® version 6 (GraphPad Software, San Diego, California, USA). In all test, value $p < 0.05$ was recognized as a significant difference [24].

3. Results and Discussion

In this study, the formulation of the VALS transdermal patch was carried out to observe the characterization of VALS transdermal patches, drug release, and drug permeation in rat skin in an *ex vivo* study. VALS transdermal patches were made in 3 different formulas using PEG 400 as a permeation enhancer with varying concentrations, namely F1 (0.5%), F2 (1%), F3 (1.5%), HPMC K-100 as a polymer matrix, and glycerin as a plasticizer. The result of VALS transdermal patch preparation can be seen in Figure 2. Based on the results of organoleptic observations, all the formulas showed that the patch preparation was transparent, had a smooth, dry surface texture, did not crack, and was odorless. This is in accordance with the characteristics of a good patch preparation: a smooth and dry surface that does not shrink over time is uniform and does not crack [25, 30].

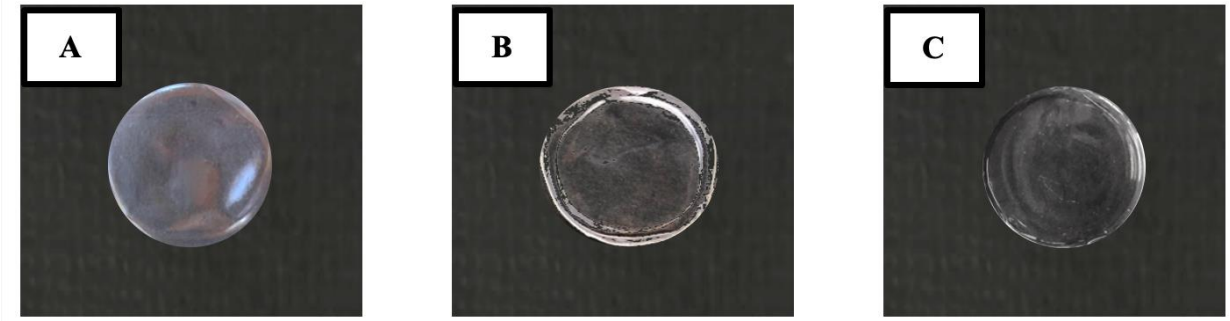

Figure 2. (**A**) F1 VALS transdermal patch; (**B**) F2 VALS transdermal patch; (**C**) F1 VALS transdermal patch.

3.1. Characterization of VALS transdermal patches.

3.1.1. Weight and thickness uniformity.

The test for uniformity of weights aimed to evaluate the consistency during the preparation process so that it will produce relatively the same product (containing the same dose) [31]. Table 2 showed the average weights ranging from 0.8 g to 1.01 g, with the mean weights for F1 = 0.8 ± 0.0 g, F2 = 0.89 ± 0.0 g and F3 = 1.01 ± 0.00 g. The results showed that the weight uniformity of each formula had a significant difference ($p < 0.05$). The difference in weight uniformity on the patch preparation may occur due to the different concentrations of the permeation enhancer (PEG 400) used. According to research conducted by [32], PEG can maintain the water content in the preparation. The more concentration used, the heavier the dosage would be.

Table 2. Weight and thickness uniformity of VALS transdermal patches means ± SD, n=3.

Formula	Average weight (g)	RSD	Average thickness (mm)	RSD
F1	0.80 ± 0.00	0.71	0.20 ± 0.00	4.84
F2	0.89 ± 0.00	0.64	0.20 ± 0.00	4.08
F3	1.01 ± 0.00	0.56	0.24 ± 0.01	4.81

Patch thickness test is very influential in releasing therapeutic substances and patient comfort or compliance. The thicker the patch, the longer the release of the drug because the drug must pass through a thicker polymer. In addition, thin patch preparations would be more comfortable to use when compared to thick patch preparations [31]. The results revealed that the average thickness for F1 and F2 was 0.20 ± 0.00 mm and for F3 was 0.24 ± 0.01 mm. According to the previous study [31], a good patch preparation requirement was not more than 1 mm. These results indicate that the resulting patch has met the requirements and has a thickness that is not significantly different ($p > 0.05$). The difference in patch thickness of each formula might be caused by the concentration of PEG 400, the area of the impression, the volume of the solution, and preparation processes such as mixing and transferring materials into molds and drying processes [24, 31]. Table 2 also showed that the % RSD of the average weight and thickness was less than 5%, indicating acceptable uniformity [24].

3.1.2. Moisture content.

The moisture content test aimed to determine the water content in preparation. The value moisture content of a good polymatrix transdermal patch preparation has a value of less than 10%. Values below 10% mean the active ingredients are protected from microbial growth [33]. Figure 3 showed the average moisture content of F1 = 3.505 ± 0.259, F2 = 8.990 ± 0.707, and F3 = 9.512 ± 0.821. Based on these results, the moisture content of each formula qualified the requirements, and there was a significant difference ($p < 0.05$). Therefore, variations in the concentration of polyethylene glycol affect the moisture content of the patch. This was probably due to polyethylene glycol having the ability to absorb water in the air, so the higher the concentration, the higher the moisture content produced [33].

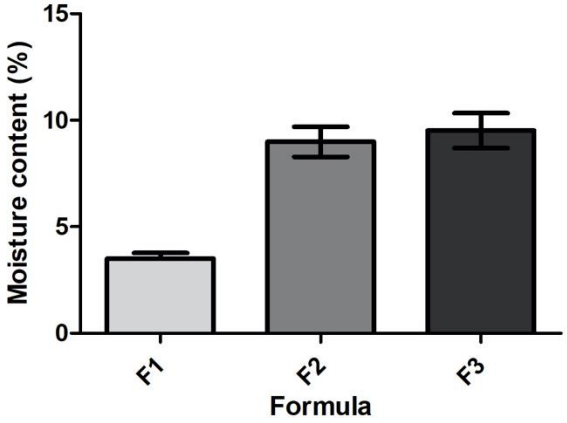

Figure 3. Moisture content of VALS transdermal patch.

3.1.3. Folding endurance.

The patch was a folding resistance test aimed to see the elasticity ability of the patch preparation [34]. The results in Table 3 showed all the formulas all formulas can last up to 300 folds. Meanwhile, in previous studies, a good patch should have more than 200-300 folding resistance[24, 35]. Based on the result above, the folding resistance of the VALS patches between the 3 formulas had a significant difference ($p < 0.05$). This is probably caused by the difference in the concentration of PEG 400 on each formula. F3 contains PEG 400 with a higher concentration than the other two formulas, so the average number of folds produced is greater. According to research conducted by [34], PEG 400 can increase the elasticity of polymatrix patches because it has flexural properties and can act as a plasticizer. In addition, HPMC

polymer in patch preparations has hydrophilic properties, which can increase the elasticity of the patch so that the formed preparation is not easily cracked or broken [36, 37].

Table 3. Folding endurance of VALS transdermal patches means ± SD, n = 3.

Formula	Folding endurance (times)
F1	356 ± 4
F2	377 ± 6
F3	396 ± 2.64

3.1.4. Drug content.

Table 4 showed that the drug content (VALS) in the patch preparation F1 = 95.26 ± 0.03%, F2 = 95.11 ± 0.06% and F3 = 96.15 ± 0.03%. The requirements for a good drug content are 95-105%, so it can be ascertained that the patch drug content qualified the requirements [38]. Based on these results, the drug content in the patch for each formula did not have a significant difference ($p > 0.05$), so the difference in the concentration of PEG 400 did not significantly affect the uniformity of the drug content in the patch preparation of each formula.

Table 4. Drug content of VALS transdermal patches means ± SD, n = 3.

Formula	Drug content (%)
F1	95.26 ± 0.03
F2	95.11 ± 0.06
F3	96.15 ± 0.03

3.2. In vitro release study.

Figure 4(a) showed the amount of drug released from the patch preparation in 8 hours at F1 = 7.756 ± 0.005, F2 = 8.043 ± 0.015 and F3 = 8.993 ± 0.015.

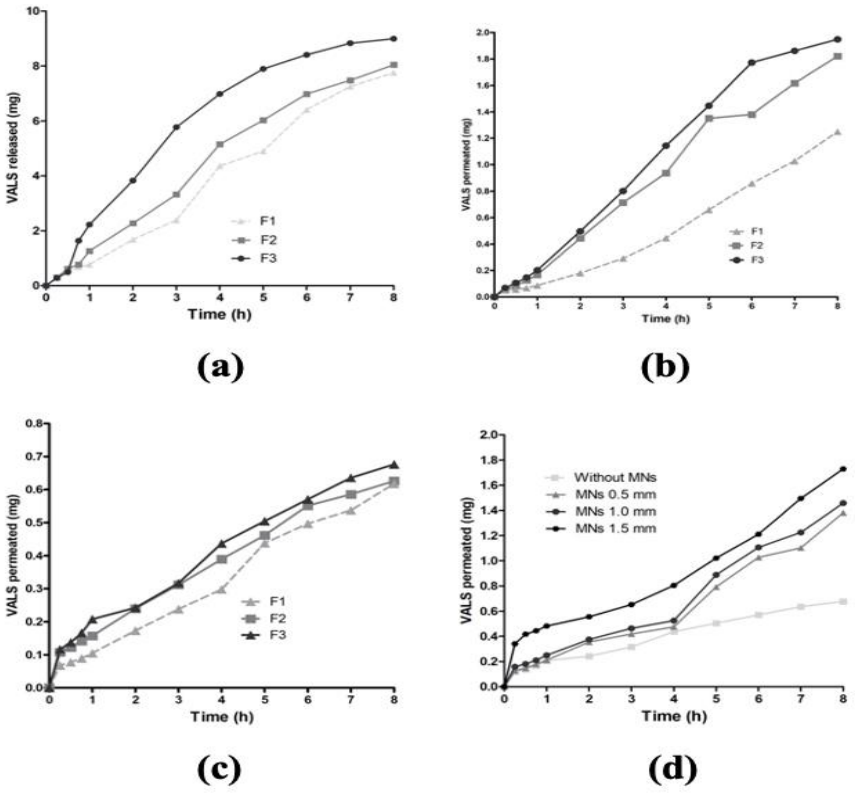

Figure 4. The result of (a) in vitro release of VALS transdermal patch; (b) in vitro permeation of VALS transdermal patch; (c) ex vivo permeation of VALS transdermal patch without MNs; (c) ex vivo permeation of F3 VALS transdermal patch with and without MNs (means ± SD., n = 3).

These results showed a significant difference ($p < 0.05$). Based on research conducted by [18, 19], polyethylene glycol 400 can increase the release of drug molecules. The greater the amount of PEG used, the greater the amount of drug released. Moreover, the addition of HPMC as a hydrophilic polymer can cause the formation of pores in the patch that is in contact with the dissolution medium so that the polymer will dissolve faster and increase drug release [37, 39].

3.5 In vitro and ex vivo permeation study

Figure 4(b) shows that the number of VALS permeated from the patch preparation in 8 hours was 1.249 ± 0.001 for F1, 1.821 ± 0.000 for F2, and 1.948 ± 0.003 for F3. Meanwhile, in Figure 4(c), the amount of drug permeated in 8 hours at F1 was 0.617 ± 0.001, F2 was 0.626 ± 0.000, and F3 was 0.676 ± 0.003. The results of both permeation tests indicated a significant difference ($p < 0.05$). It has been previously reported that PEG 400, as a permeation enhancer, can increase the permeation of drug molecules through the skin [18, 19]. PEG works by entering the SC layer of mammalian skin and changing its solubility properties so that it can increase drug permeation [40].

Considering the results obtained in physical characteristics, *in vitro* release, *in vitro* permeation, and *ex vivo* permeation without MNs, F3 (PEG 400 1.5%) was selected as the optimum formula, which will be further evaluated in the *ex vivo* permeation with MNs test. This test uses mouse skin as a biological membrane and MNs in the form of Dermaroller® with different needle length variations. The length of the needles used were 0.5 mm, 1.0 mm, and 1.5 mm to see the effect of MNs needle length on VALS permeation.

Figure 4(d) shows the amount of VALS permeated up to 8 h from the patch without combining MNs of 0.676 ± 0.003 mg. While the patch combined with 0.5 mm MNs showed the amount of drug permeated by 1.381 ± 0.001 mg, the combination with 1.0 mm MNs was 1.458 ± 0.001 mg, and the combination with 1.5 mm MNs was 1.728 ± 0.001 mg. Based on the results obtained, there was a significant increase in the number of permeated VALS ($p < 0.05$) when the preparation was combined with MNs. This can increase the level of VALS that enters the system. In addition, it is seen that the longer the size of the MNs used, the greater the amount of drug that can be permeated. MNs can increase drug permeation in transdermal preparations by forming micropores on the skin. Therefore, drug molecules can easily pass through the SC layer (stratum corneum), which is known to be the largest barrier component in the skin [7]. According to a previous study, it has been reported that the longer the needle size of MNs, the greater the amount of drug that will permeate [20].

4. Conclusions

In conclusion, the formulation of the HPMC-based VALS transdermal patch and PEG 400 as a permeation enhancer has qualified all requirements for good physical characteristics and drug release. Moreover, the combination of VALS transdermal patches with MNs in ex vivo studies also increased the permeation of VALS through the stratum corneum, leading to an increase in their bioavailability. However, to support the research data that has been obtained, it is necessary to carry out several tests such as stability, skin irritation, pharmacokinetics, and in vivo studies.

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Conflicts of Interest

The authors declare no conflict of interest.

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