Available online at
https://ijpncs.uitm.edu.my/index.php/en/

IJPNaCS International Journal of Pharmaceuticals, Nutraceuticals and Cosmetic Science
e-ISSN: 2682-8146

International Journal of Pharmaceuticals, Nutraceuticals and Cosmetic Science
9(1) 2026, 81-96

International Journal of Pharmaceuticals, Nutraceuticals and Cosmetic Science

Effects of ethyl cellulose and polyvinyl alcohol mass ratio on the release and permeation profiles of a simvastatin-loaded transdermal system

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ARTICLE INFO

Article history:
Received 28 February 2026
Revised 03 May 2026
Accepted 10 May 2026
Online first
Published 30 May 2026

Keywords:
Matrix-type transdermal system,
Release kinetic modeling,
Solvent casting method,
Polymer

DOI:
10.24191/IJPNaCS.v9i1.05

ABSTRACT

Simvastatin (SMV), a widely prescribed drug for the treatment of hypercholesterolemia, has low oral bioavailability due to poor aqueous solubility and extensive first-pass metabolism. Transdermal delivery of this drug is a promising alternative to increase its bioavailability. As part of preliminary formulation studies for a matrix-type transdermal system for SMV, this study aimed to investigate the effects of different mass ratios of ethylcellulose (EC) and polyvinyl alcohol (PVA) on SMV release and permeation. *In vitro* drug release was performed via USP dissolution apparatus 5. *In vitro* permeation was performed using a diffusion cell with Strat-M® as membrane. The formulation with the balanced release and permeation characteristics was further evaluated for thickness, weight uniformity, folding endurance, moisture content, SMV content, and adhesion characteristics. The formulations showed similar sustained release profiles within 24 h, with maximum release (95.30 ± 2.96%) exhibited by F4 containing 7:3 EC:PVA ratio, which was significantly different from formulations F1-F3 containing lower amounts of EC. Kinetic modeling shows similar non-Fickian release of SMV from all the formulations. In the permeation studies, F5 containing 9:1 EC:PVA ratio showed the highest quantity of SMV permeated (16.38%) and flux (0.6964 µg/cm^2/h), but this was not statistically different from the permeation characteristics of F4. Based on release and permeation performance, formulation F4 is promising for further development. It also exhibited satisfactory physicochemical characteristics overall, but the adhesion performance remains to be improved in optimization studies.

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1. INTRODUCTION

A transdermal drug delivery system (TDDS) is a non-invasive drug delivery system used to administer drugs systemically through the skin. It offers the advantages of bypassing first-pass metabolism, thereby increasing the bioavailability of the drug, and reducing side effects such as irritation of the gastrointestinal tract (Sabbagh & Kim, 2022), making it an attractive alternative to oral drug delivery. Another benefit of TDDS is improved patient compliance through the reduction in dosing frequency by controlling the rate of release and permeation of the drug through the skin. This also allows effortless termination of drug therapy, especially when the patient relies on self-administration (Rastogi & Yadav, 2012).

Simvastatin (SMV) is a cholesterol-lowering drug that works by blocking the active site of HMG-CoA reductase, hindering the conversion of HMG-CoA to mevalonic acid, one of the precursors of cholesterol (Ward et al., 2019). It is one of the most widely prescribed statins to treat hypercholesterolemia and is commonly available as a solid dosage form intended to be administered orally. However, a major problem with simvastatin oral administration is its poor bioavailability (<5%) due to its poor aqueous solubility (6.3 µg/mL), lipophilicity (logD at pH 7.4 = 1.5–1.75) and extensive first-pass metabolism (oral $t_{1/2}$ = 2 h) (Korani et al., 2019; Krishnam Raju et al., 2014). The criteria for drugs that can be formulated into TDDS include aqueous solubility of less than 1 mg per mL, lipophilicity of greater than 1 but less than 3, molecular weight of less than 500 Da, melting point of less than 200 °C, and short oral half-life. The molecular weight of SMV is 418.56 g/mol and the melting point is 135–138°C (El-Say et al., 2015; Parhi & Padilam, 2018; Parhi & Suresh, 2016).

In this study, SMV was formulated into a matrix-type transdermal system wherein the drug was mixed with hydrophilic or lipophilic polymers, or a combination of these polymers (Pastore et al., 2015; Rastogi & Yadav, 2012). The polymer matrix is the backbone and one of the major components of a transdermal system, as the nature and concentration of these polymers control the rate of drug delivery as well as the mechanical properties of the formulation (Parhi & Suresh, 2016). The polymers used for the matrix are ethylcellulose (EC), a hydrophobic polymer, and polyvinyl alcohol (PVA), a hydrophilic polymer. The matrix was also mixed with a permeation enhancer (isopropyl myristate), a plasticizer (dibutyl phthalate), and an adhesive polymer (acrylates copolymer). The study aimed to investigate the effects of varying the mass ratio of EC and PVA on the release and permeation profiles of SMV from a transdermal system as a preliminary step toward formulation optimization.

2. MATERIAL & METHODOLOGY

2.1 Materials

The synthetic polymers ethyl cellulose (EC; Sigma-Aldrich, USA) and polyvinyl alcohol (PVA; degree of saponification: 97–100%, Tokyo Chemical Industry, Japan) served as matrix-forming polymers for the TDDS. Isopropyl myristate (IPM; SBS Philippines Corporation, Quezon City, Philippines), dibutyl phthalate (DP; Sigma-Aldrich, Russia), and acrylates polymer (Repoly 100, Guangzhou Reachin Chemical Co., Ltd, China) were used as permeation enhancer, plasticizer, and adhesive, respectively. All reagents used were of analytical grade and procured from local suppliers. SMV (content: 100.4%), which served as the active ingredient of the transdermal system, was procured locally (MDLD Interchemical Industries Inc., Quezon City, Philippines).

https://doi.org/10.24191/IJPNaCS.v9i1.05

2.2 Construction of the calibration curve for SMV

Fifty milligrams (50 mg) of standard SMV was dissolved in dimethyl sulfoxide (DMSO) and filled to 100 mL volume. From this stock solution, aliquots were withdrawn and diluted with PBS pH 7.4 in 50 mL volumetric flasks to prepare solutions with concentrations of 1, 13, 25, 37, 49, 61, 73, and 85 µg/mL. The standard solutions were analyzed using a developed HPLC (Waters Alliance e2695) method for SMV TDDS (Manalo-Cabalinan & Bulatao, 2026; Manalo-Cabalinan et al., n.d.) (linearity: 1–5 µg/mL; r^2 = 0.9918–0.9995) with modifications. The analysis was run using a C18 column (4.6 mm ×150 mm, 5 µm) and acetonitrile:phosphate buffer pH 4.5 (65:35) mobile phase at a flow rate of 1.5 mL/min for 8 min. The column temperature was maintained at 45°C and the injection volume was set to 10 µL. SMV was detected using a PDA detector at 238 nm to create the calibration curve ($y = 181810x + 1611.8$, $r^2 = 0.9997$).

2.3 Fabrication of simvastatin-loaded matrix-type transdermal system

A polymer solution was prepared by dissolving PVA in 2.5 mL of 80% DMSO in distilled water under stirring for 6 min at 95 °C. EC was dissolved in 4 mL ethanol and was added slowly to the PVA solution under continuous stirring for 13 min. These mixing conditions were applied to ensure the complete dissolution of the polymers prior to mixing. Acrylates copolymer (AC), isopropyl myristate (IPM) and dibutyl phthalate (DP) were added thereafter. The mixture was cooled to a temperature below 70°C prior to the addition of SMV powder to prevent its degradation. Table 1 shows a summary of the polymer composition of the five formulations evaluated in the study.

Table 1. Polymer composition of SMV transdermal system

Formulation code	EC:PVA mass ratio	EC (mg)	PVA (mg)
F1	1:9	27	243
F2	3:7	81	189
F3	5:5	135	135
F4	7:3	189	81
F5	9:1	243	27

After ensuring all ingredients were completely dissolved, the solution was removed from heat and was poured into the mold. This was followed by air drying for 24 h, vacuum drying for 6 h, and drying in a desiccator for 16 h to allow solvent evaporation. The molded product was stored in a desiccator until further use.

The backing membrane was prepared based on the work of Idrees et al. (2014) with modifications. One thousand four hundred (1400) mg of PVA was dissolved in 20 mL of distilled water. The solution was mixed for 40 min at 60 rpm while being heated up to 87 °C. After ensuring all PVA were completely dissolved, the solution was allowed to cool for 2 min before being transferred into a Petri dish. Once transferred and evenly distributed on a Petri dish, a glass mold for the matrix was placed on the backing layer to ensure that leaks from the matrix were avoided. For ease of removal of the backing membrane, the Petri dish was previously spotted with candle wax. Finally, the solution was air-dried for 24 h and stored in a desiccator until further use.

https://doi.org/10.24191/IJPNaCS.v9i1.05

2.4 In vitro simvastatin release profiling

The release test of SMV from the fabricated transdermal systems was adapted from previously described literature (Madgulkar et al., 2020) with modifications. The vessels were each filled with 900 mL of the dissolution medium (pH 7.4 PBS), then equilibrated to 32 ± 0.5°C. The SMV transdermal systems were then affixed to the disk assembly of the USP Apparatus 5. The formulations were placed firmly and as flat as possible, with the release side facing upwards. When the instrument temperature reached 32 ± 0.5°C, the formulations were placed in the vessels. Next, the paddle attachments were fixed into the dissolution equipment. The paddles were then lowered to a distance of 25 ± 2 mm from the surface of the disk assembly and then set at 100 rpm. The timer was started immediately after the paddles started rotating. From each vessel, 10 mL of dissolution medium was withdrawn at predetermined intervals (0.25, 0.5, 1, 2, 4, 8, 12, 24 h), followed by replenishment with an equal amount of fresh dissolution medium. The medium was withdrawn at the area more than 1 cm away from the vessel and between the top of the blade and the surface of the dissolution medium. An aliquot of the withdrawn medium was then analyzed using HPLC with the same parameters described in Section 2.2.

The data collected were fitted into various models such as Higuchi, first-order, zero-order, Korsmeyer-Peppas, and Hixson-Crowell models to describe the release kinetics and mechanism of drug diffusion from the formulation. The mechanism of drug release was then determined by the model that fits the data (al Hanbali et al., 2019). The Higuchi model is given by the following equation where Q is the amount of drug released, t is time, and K_H is the Higuchi Dissolution constant.

$$Q = K_H \times t^{1/2}$$

The zero-order model is given by the equation, where Q_t is the amount of drug dissolved in time *t,* Q_0 is the initial amount of the drug in solution, and K_0 is the zero-order release constant (concentration/time).

$$Q_t = Q_0 + K_0 t$$

The first-order model is given by the equation where C_0 is the initial drug concentration, K is the first-order constant (t^{-1}), and t is the time.

$$\log C = logC_0 - \frac{Kt}{2.303}$$

The Peppas and Korsmeyer model is given by fitting the initial 60% release data to the following equation where $\frac{M_t}{M_\infty}$ is the ratio of drug released, t is time, K is the release rate constant, n is the value used to characterize release for cylindrical matrices. The value of n depends on the drug transport mechanism, namely Fickian, non-Fickian, Case II, or Super case II transport (Dash et al., 2010).

$$\frac{M_t}{M_\infty} = Kt^n$$

https://doi.org/10.24191/IJPNaCS.v9i1.05

The data were fitted to the models using the DDSolver in MS Excel. Selection of the model that best describes the release behavior of the formulations was based on the highest r^2, minimum Akaike Information Criterion (AIC), and maximum model selection criterion (MSC) values (Zhang et al., 2010).

2.5 In vitro permeation test

The permeation test was done using a diffusion apparatus connected to a circulating water bath set at 32 °C. Each apparatus was filled with 13 mL of PBS pH 7.4 with 0.5% (w/v) SDS and was stirred by a magnetic stirrer at 80 rpm. After equilibration, the Strat-M® membrane was placed in each apparatus with its shiny side facing the donor compartment. A 1×1 cm^2 test sample cut from the transdermal system was then applied to the membrane, secured by the donor compartment, and fastened with a clamp. Five (5) mL of the medium was put in the donor compartment to facilitate dripping and permeation. One (1) mL of the medium in the receptor compartment was withdrawn from each diffusion cell at time points 0.25, 0.5, 1, 2, 4, 8, and 24 h. For every 1 mL withdrawn, 1 mL of fresh and previously incubated medium was added to replenish the system. Withdrawn solutions were analyzed using the aforementioned HPLC method to determine the percentage of SMV that permeated the membrane at each time point. The flux or the rate of SMV delivery through the membrane was determined from the slope of linear points in the cumulative drug permeation graphs.

2.6 Physicochemical properties of simvastatin transdermal patch

The formulation with sustained release and the maximum amount of SMV released was further evaluated for its physicochemical properties.

2.6.1 Thickness

Three (3) samples were taken, and the thickness was measured using a digital micrometer screw gauge (Mitutoyo IP65 Coolant Proof Digimatic Micrometer, Japan) at five (5) different areas in the formulation, followed by the calculation of the mean thickness and standard deviation of multiple readings.

2.6.2 Weight uniformity

Uniformity of weight was determined by weighing three (3) individual samples, followed by the calculation of their average weight and standard deviation.

2.6.3 SMV content

The fabricated SMV transdermal system was dissolved in 100 mL DMSO and stirred by a magnetic stirrer until it became homogenous. An aliquot of the solution was then withdrawn and filled to 50 mL with PBS. The sample was analyzed using the same HPLC procedure described in Section 2.2.

2.6.4 Folding endurance

Folding endurance was determined by counting the number of times that the sample could be folded until it breaks or cracks.

https://doi.org/10.24191/IJPNaCS.v9i1.05

2.6.5 Moisture content

The moisture content of the transdermal system was determined by accurately weighing the patch before and after placing the patch in a desiccator for 24 h at room temperature. The percentage moisture was calculated using Eq. (1).

$$\text{Moisture Content (\%)} = \frac{\text{Initial mass-Final mass}}{\text{Initial Mass}} \times 100 \quad (1)$$

2.6.6 Shear Adhesion Test

A simplified shear adhesion test was done which was modified from the test made from previously described literature (Mehdizadeh et al., 2004). The portion of the formulation three (3) cm from the center was allowed to adhere to a stainless-steel plate and was pressed with a flat surface that could encompass the entire sticking area of the patch. Pressure was applied three times each for 10 s. A 20 g standard weight was attached to the bottom of the transdermal patch via 2 clips. Adhesion was measured as the duration, in seconds, that the patch remained attached to the stainless-steel plate.

2.7 Statistical analysis

Data are presented as mean ± standard deviation. Statistical analysis was performed using JASP 0.96 (The JASP Team, The Netherlands). Normality of the data was assessed using the Shapiro-Wilk test, while homogeneity of variances was evaluated using Levene's test. Differences in the cumulative percentage of SMV released after 24 h among formulations were analyzed using one-way analysis of variance (ANOVA). When a significant difference was detected, post hoc multiple comparisons were performed using Tukey's HSD with Scheffe correction. If the assumptions for one-way ANOVA were not met, differences among formulations were analyzed using the Kruskal-Wallis test followed by Dunn's post hoc multiple comparison test. A p-value of less than 0.05 was considered statistically significant.

3. RESULTS

3.1 In vitro SMV release

The cumulative percentage of SMV released from each formulation was plotted against time (Fig. 1). All formulations exhibited sustained release behavior, with more than 50% of SMV released only after 12 h. No burst release was observed, suggesting that SMV was gradually released from the polymeric matrix. Among the formulations, F4, containing an EC:PVA mass ratio of 7:3, showed the highest mean cumulative SMV release after 24 h. One-way ANOVA showed a statistically significant difference in the cumulative percentage of SMV released after 24 h among the formulations ($p < 0.001$). Post hoc multiple comparisons using Tukey's HSD with Scheffe correction showed that F4 released significantly more SMV than F1 ($p < 0.001$), F2 ($p = 0.001$), and F3 ($p = 0.010$). Although F4 had the highest mean cumulative release, its release was not statistically different from F5 ($p = 0.065$). F5 also showed significantly higher release than F1 ($p = 0.048$), while the remaining formulation comparisons were not statistically significant. These findings indicate that the EC:PVA ratio influenced SMV release. Thus, F4 may be considered the best-performing

formulation based on its numerically highest release and statistically higher release relative to F1, F2, and F3.

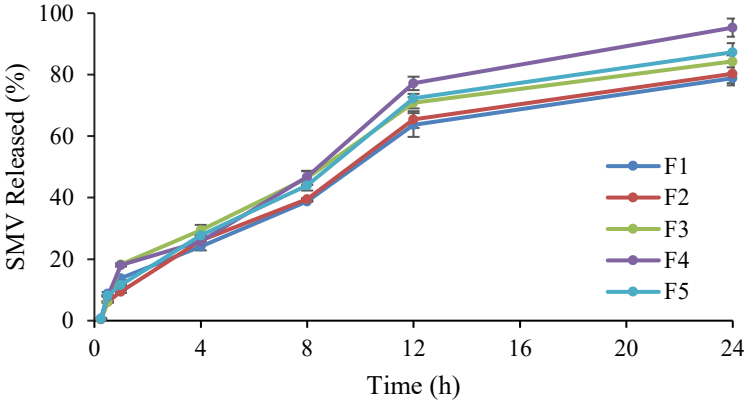

Fig 1. Cumulative percentage of SMV released from the formulated SMV transdermal systems over 24 h.

The in vitro SMV release data of formulations F1–F5 were fitted to zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell models. The calculated release constants, adjusted r^2, Akaike information criterion (AIC), and model selection criterion (MSC) values are summarized in Table 2. Among the models evaluated, the first-order model provided the best fit for F1, F2, F3, and F5, as indicated by the highest adjusted r^2 values and MSC values, together with the lowest AIC values. The adjusted r^2 values for the first-order model were 0.9704, 0.9829, 0.9718, and 0.9802 for F1, F2, F3, and F5, respectively. For F4, the Hixson-Crowell model showed the best fit, with an adjusted r^2 of 0.9710, AIC of 39.8567, and MSC of 3.2605. The zero-order model showed comparatively lower adjusted r^2 values across all formulations, ranging from 0.8001 to 0.8674. For the Higuchi model, adjusted r^2 values ranged from 0.9425 to 0.9568, while the Korsmeyer-Peppas model showed adjusted r^2 values ranging from 0.9560 to 0.9645. The release exponent values obtained from the Korsmeyer-Peppas model ranged from 0.565 to 0.629 across formulations.

Table 2. In vitro release kinetic parameters of SMV from formulations F1–F5 fitted to different mathematical models.

Model	Sample	Parameter	r^2 adjusted	AIC	MSC
Zero order	F1	$k_0 = 3.846$	0.8488	48.5731	1.6087
	F2	$k_0 = 3.926$	0.8674	48.3547	1.7422
	F3	$k_0 = 4.224$	0.8001	51.7906	1.3310
	F4	$k_0 = 4.634$	0.8597	50.9219	1.6798
	F5	$k_0 = 4.297$	0.8529	50.1907	1.6405
First order	F1	$k_1 = 0.072$	0.9704	37.0637	3.2529
	F2	$k_1 = 0.074$	0.9829	33.9270	3.8033
	F3	$k_1 = 0.089$	0.9718	38.0817	3.2894
	F4	$k_1 = 0.099$	0.9634	41.4290	3.0359
	F5	$k_1 = 0.088$	0.9802	36.1312	3.6490
Higuchi	F1	$k_H = 15.782$	0.9535	40.2467	2.7982
	F2	$k_H = 16.041$	0.9474	41.8797	2.6672
	F3	$k_H = 17.516$	0.9568	41.0547	2.8647
	F4	$k_H = 18.941$	0.9425	44.6582	2.5746
	F5	$k_H = 17.612$	0.9485	42.8968	2.6825
Korsmeyer -Peppas	F1	$k_{KP} = 12.036$ $n = 0.605$	0.9630	39.1566	2.9539

https://doi.org/10.24191/IJPNaCS.v9i1.05

	F2	k_{KP} = 11.463 n = 0.629	0.9645	39.8267	2.9605
	F3	k_{KP} = 14.800 n = 0.565	0.9567	41.6981	2.7728
	F4	k_{KP} = 13.704 n = 0.624	0.9560	43.5067	2.7391
	F5	k_{KP} = 13.070 n = 0.615	0.9608	41.6263	2.8640
Hixson-Crowell	F1	k_{HC} = 0.020	0.9580	39.5410	2.8990
	F2	k_{HC} = 0.021	0.9729	37.0760	3.3534
	F3	k_{HC} = 0.025	0.9578	40.8674	2.8914
	F4	k_{HC} = 0.028	0.9710	39.8567	3.2605
	F5	k_{HC} = 0.025	0.9768	37.2340	3.4915

Note: k_0 = zero-order release constant; k_1 = first-order release constant; kH = Higuchi release constant; kKP = Korsmeyer-Peppas release constant; n = release exponent; kHC = Hixson-Crowell release constant; AIC = Akaike information criterion; MSC = model selection criterion. The best-fitting model was selected based on the highest adjusted r^2 and MSC values and the lowest AIC value.

3.2 In vitro permeation test

The cumulative percentage of SMV permeated through the skin was plotted against time (Fig. 2). All formulations showed a slow initial permeation phase followed by increased permeation beginning at approximately 8 h. Among the formulations, F5, containing the highest EC:PVA ratio of 9:1, showed the highest mean flux at 0.6964 μg/cm²/h (Table 3) and the highest cumulative SMV permeation after 24 h at 16.38%. The Kruskal-Wallis test showed a statistically significant difference in cumulative SMV permeation after 24 h among the formulations ($p = 0.009$). Post hoc multiple comparisons showed that F5 was significantly higher than F1 ($p = 0.001$) and F3 ($p = 0.014$), but was not significantly different from F4 ($p = 0.411$). F4 was also significantly higher than F1 ($p = 0.014$). The remaining pairwise comparisons were not statistically significant. Although F5 showed the highest mean flux and cumulative permeation, its difference from F4 was not statistically significant. Thus, the selection of F4 for further physicochemical evaluation was supported by its comparable permeation performance, together with its overall formulation characteristics.

https://doi.org/10.24191/IJPNaCS.v9i1.05

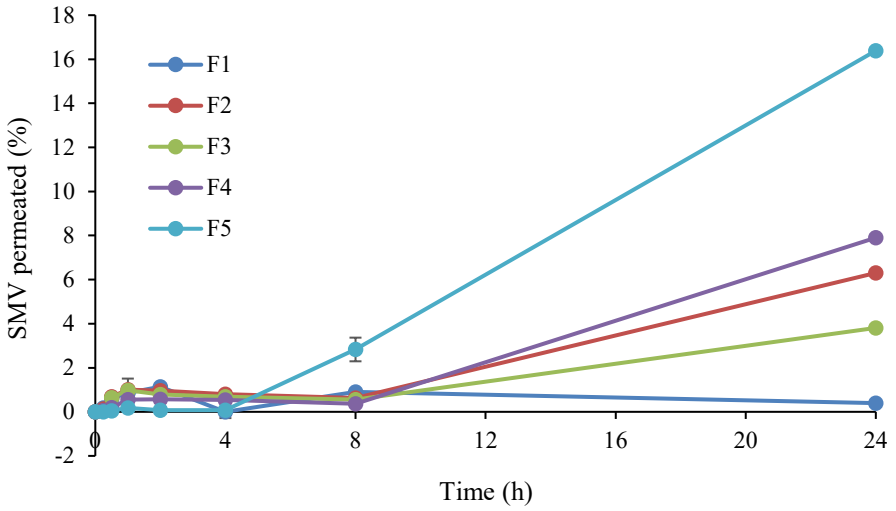

Fig 2. Cumulative percentage of SMV permeated from formulations F1–F5 over 24 h

Table 3. Summary of permeation characteristics of different SMV transdermal systems.

Formulation	Flux (µg/cm^2/h)
F1	0.5611
F2	0.2681
F3	0.1698
F4	0.6671
F5	0.6964

3.3 Physicochemical properties of the fabricated simvastatin transdermal system

Formulation F4, which exhibited sustained and maximum release in 24 h, was evaluated for its physicochemical properties. The mean ± SD of the properties are summarized in Table 4.

Table 4. Summary of physicochemical properties of F4 (n=3)

Property	Mean ± SD
Thickness (mm)	1.05 ± 0.08
Folding endurance (no. of folds)	892.33 ± 41.51
Weight (g)	2.57 ± 0.12
Moisture content (%)	4.57 ± 0.60
Drug content (%)	100.43 ± 5.72
Adhesion (seconds)	13.53 ± 7.56

https://doi.org/10.24191/IJPNaCS.v9i1.05

4. DISCUSSION

SMV was formulated into a matrix-type transdermal system using varying mass ratios of EC and PVA as the polymers. The nature and concentration of polymers in the matrix were hypothesized to affect the rate of drug delivery and the mechanical properties of the formulation. Using a combination of hydrophilic and lipophilic polymers in the matrix would allow the adjustment of the partitioning of the drug from the formulation to the skin to control drug delivery. Several studies explored different types of polymers in fabricating SMV into transdermal systems, such as EC:PEG400 (Anod et al., 2018), a mixture of different grades of Eudragit (El-Say et al., 2015; França et al., 2022), and mixtures of HPMC and Eudragit (Ananthu & Vijetha, 2022). So far, no study has explored the combination of EC and PVA for SMV and the effects of its mass ratios on release and permeation. PVA, a hydrophilic polymer, is often used for sustained drug delivery due to its swelling properties that lead to the formation of a gel-like polymer network that increases diffusion pathways, slowing down drug release (Kandavilli et al., 2002). However, unwanted burst release of the drug may occur when hydrophilic polymers are used primarily due to rapid swelling, polymer chain dissolution in the release medium, matrix erosion due to the hydrophilicity of the polymer, and increased drug mobility within the matrix (Alcântara et al., 2012; Das et al., 2022; Siepmann & Siepmann, 2008). On the other hand, EC, a lipophilic polymer, is non-swellable and the release of drugs depends on the porosity of the lipophilic matrix. Solely using lipophilic polymers, however, may result in insufficient or very slow release of drug from the formulation (Das et al., 2022).

4.1 In vitro drug release

The cumulative drug release of formulations 1-5 are presented in Fig. 1. For transdermal systems, maximum and sustained release of the API are preferred for diffusion to happen (Madgulkar et al., 2020). From the release profiles, it is evident that the combination of EC and PVA in a matrix-type system exhibits sustained release within 24 h with no burst release. Formulation F4, with an EC:PVA ratio of 7:3 has shown maximum SMV released (95.30 ± 2.96%) and statistical difference with formulations F1-F3. This means that increasing EC while decreasing PVA until a ratio of 7:3 resulted in increased SMV release. The trend observed is in contrary with many studies incorporating hydrophobic drugs in a matrix of hydrophilic:lipophilic polymers. In these studies, the release was found to increase when the hydrophilic polymer is increased while decreasing the concentration of the hydrophobic polymer, which is mainly due to the higher attraction of water of the hydrophilic polymers used (Das et al., 2022; El-Say et al., 2015; Latif et al., 2021; Siepmann & Siepmann, 2008). The slower release rate observed in F1-F3 containing higher concentrations of PVA may be because of the higher diffusional path length in formulations due to its swelling ability when exposed to the release medium (Patel et al., 2009). Increasing EC further, as in the case of F5 (9:1 EC:PVA ratio), did not have a significant effect on the release of SMV. Therefore, the 7:3 mass ratio of EC:PVA is a good balance of lipophilicity and hydrophilicity for sustained and maximum release of SMV.

The drug transport mechanism was based on the release exponent obtained by fitting the release data in the Korsmeyer-Peppas model (Dash et al., 2010). The drug release of F1, F2, F3, and F5 followed first-order release kinetics with non-Fickian drug transport mechanism. On the other hand, F4 followed the Hixson-Crowell release kinetics with non-Fickian drug transport. According to Fu and Kao (2010), matrix-

https://doi.org/10.24191/IJPNaCS.v9i1.05

type devices usually follow Fickian drug transport, which is dependent on the degree of swelling, diffusion distance, and ultimately the concentration gradient. In this study, all formulations with EC and PVA matrices followed non-Fickian drug transport. This indicates that release kinetics of F1-F5 does not solely depend on the concentration gradient but is also affected by the characteristics of the formulation. The combination of hydrophilic and lipophilic polymers theoretically will affect drug release, which contributes to non-Fickian diffusion. This may be due to the in situ formation of additional pores in the matrix and an increase in diffusion path length when hydrophilic polymers are dissolved in the release medium (Patel et al., 2009). In the formulation, PVA, which is prone to swelling, chain relaxation, and increased chain mobility when exposed to the release medium, allows diffusion of the drug from the matrix to the release medium (Siepmann & Siepmann, 2008).

4.2 In vitro permeation

The permeation characteristics of SMV from the transdermal system were investigated using a Strat-M® diffusion membrane. Strat-M® is a synthetic membrane comprised of several layers mimicking the structure of human skin – a tight top layer resembling the stratum corneum, followed by two layers of porous polyether sulfone and a single layer of polyolefin non-woven fabric. Aside from the structure, the layers also contain a blend of synthetic lipids in amounts similar to those in human skin. Several studies have tested the permeability of different compounds and formulations in Strat-M® membrane and the determined diffusion characteristics, and permeability coefficients have a high correlation with the results obtained in human and animal skin (Haq et al., 2018; Uchida et al., 2015). Hence, this membrane was used to determine the permeation characteristics of SMV in the fabricated transdermal system.

The permeation behaviour of SMV appears to be influenced by the balance between the lipophilic and hydrophilic components of the polymeric matrix rather than by EC content alone. While EC-dominant formulations tended to show greater SMV permeation, this relationship should not be interpreted as strictly linear because the permeation performance of F5 was statistically comparable to F4. The hydrophobic nature of EC and the lipophilic character of SMV may favor drug partitioning from the matrix toward the membrane, while PVA may contribute to matrix hydration and drug mobility. Thus, the EC:PVA ratio may affect permeation by modifying both drug–polymer interactions and the ability of SMV to partition from the hydrated matrix into the membrane. However, permeation is also influenced by other formulation and experimental factors, including the distribution of SMV within the matrix, the activity of the permeation enhancer, and the adhesive-matrix structure. Therefore, further mechanistic studies are needed to confirm the specific contribution of EC to SMV transport across the membrane.

4.3 Physicochemical characteristics of the transdermal system

The thickness of the formulation is considered a critical quality attribute, for it can affect permeation and release of a drug. A thicker matrix can deliver higher amounts of drug to the skin over a relatively longer application time due to a higher amount of drug available for permeation from the formulation. However, a thicker matrix has a higher tendency to cause “cold flow” which is defined as the migration of adhesive beyond the boundaries of formulation which may lead to the decrease in drug flux across the skin (Hossain et al., 2011; Wokovich et al., 2015). Hence, the thickness of a transdermal system can neither be too thick

https://doi.org/10.24191/IJPNaCS.v9i1.05

nor too thin and must be constant to ensure low variability in terms of drug flux. The results show that the formulations have an average thickness of 1.05 mm with a standard deviation of 0.08 mm. In addition, the average weight was 2.57 g with a standard deviation of 0.12 g. The standard deviation for weight and thickness was low. Hence, the method for producing them could be said to be reproducible.

The combination of the polymer matrix with a plasticizer (dibutyl phthalate) resulted in satisfactory folding endurance which indicates that the formulations had optimum flexibility and were not brittle. Moreover, the folding endurance was found to be more than 150 folds which revealed that the formulations could withstand mechanical pressure (Cherukuri et al., 2017). Plasticizers work by decreasing the tensile strength of the film and making it more flexible through diminishing intermolecular forces between polymeric chains. This results in a better folding endurance of transdermal system (Parhi & Suresh, 2016).

The moisture content of transdermal systems should be between 2 and 10% for optimal mechanical properties and a good drug release pattern (Shabbir et al., 2017). Moreover, moisture is required to maintain stability, reduce brittleness, prevent bulkiness, and reduce susceptibility to microbial contamination of formulation. The percentage moisture content (4.57 ± 0.60%) was found to be within the acceptable moisture content range.

Drug content assay was also done to ensure 10 mg of SMV was loaded in each transdermal system. Results showed that all three formulations passed the 90–110% acceptance criterion for a 10 mg SMV TDDS, with a standard deviation of 5.72%. Adhesion is a critical quality attribute of a TDDS because the adhesive layer ensures intimate contact with the skin and supports delivery of the intended drug dose. According to the USP (United States Pharmacopeial Convention, 2023), adhesives used in transdermal systems should allow easy removal of the release liner before application, adhere properly to the skin upon gentle pressure, maintain adhesion throughout the prescribed period of use, and allow removal at the end of use without leaving residue, damaging the skin, or causing other undesirable effects.

In the present study, the simplified shear adhesion test showed an adhesion time of 13.53 ± 7.56 s, indicating poor adhesive performance of the transdermal system. This low value suggests that the formulation may not maintain sufficient contact with the skin during application, which is a critical limitation because inadequate adhesion can lead to premature detachment, reduced residence time, and inconsistent drug delivery. Thus, although the formulation showed promising in vitro release and permeation behaviors, its adhesive property remained insufficient for practical transdermal application. This limitation may be related to the type or concentration of the adhesive component used in the formulation, as well as the overall polymeric matrix composition, which may not have provided adequate tack or cohesive strength. Hence, further formulation work is needed to optimize the adhesive system, including adjustment of the adhesive concentration or incorporation of more suitable pressure-sensitive adhesive components. In addition, future studies should employ more appropriate and standardized adhesion tests, such as tack, peel adhesion, release liner peel, and shear adhesion tests, to better characterize the adhesive and cohesive performance of the transdermal system. Another limitation of the study is that the exact molecular weight of PVA and viscosity grade of EC were not available from the product records. These polymer specifications may influence film formation, matrix hydration, mechanical strength, and drug release, and permeation behavior. Future formulation studies should report complete polymer specifications, including molecular weight, viscosity grade, and other supplier-provided quality attributes, to improve reproducibility and facilitate comparison across studies.

https://doi.org/10.24191/IJPNaCS.v9i1.05

5. CONCLUSION

The present study demonstrated that varying the EC:PVA mass ratio influenced the in vitro release and permeation behaviors of SMV from the fabricated matrix-type TDDS. All formulations showed sustained SMV release without an initial burst effect, indicating the ability of the EC:PVA polymer blend to influence SMV release from the transdermal system. Among the formulations, F4, containing a 7:3 EC:PVA ratio, showed the highest mean cumulative SMV release and was significantly higher than F1, F2, and F3. Although F5, containing a 9:1 EC:PVA ratio, showed the highest mean permeation and flux, its permeation performance was not statistically different from F4. Thus, F4 was identified as the lead formulation for further development because it provided a more balanced performance in terms of release behaviour and comparable permeation to F5.

However, the adhesive performance of F4 remains a major limitation. The low shear adhesion value indicates that the formulation, in its current form, may not maintain adequate contact with the skin during application. Therefore, F4 should not yet be considered a final or fully suitable transdermal patch formulation, but rather a promising formulation candidate that requires further optimization. Future work should focus on improving the adhesive system, including the type and concentration of pressure-sensitive adhesive components, while also evaluating the effects of permeation enhancer and plasticizer levels on release, permeation, and mechanical performance. More standardized adhesion tests, such as tack, peel adhesion, and shear adhesion studies, should also be included to ensure that the optimized SMV transdermal system can meet the functional requirements for practical transdermal application.

ACKNOWLEDGEMENTS/FUNDING

We are grateful to the National Institutes of Health of the University of the Philippines Manila (Project Code: 2023–015) for financially supporting this study. The authors also thank Asst. Prof. Clinton B. Gomez for his assistance in the statistical analysis of the release and permeation data.

CONFLICT OF INTEREST STATEMENT

The authors declared that they have no conflicts of interest to disclose.

AUTHORS' CONTRIBUTIONS

CDRDS, IMEA, RJRG, TLDRR, RKAQ, RAMMC, BPIB: Conceptualization, Data curation, Experimentation, Visualization, Data analysis, Writing – original draft. **RKAQ, RAMMC, BPIB**: Supervision, Resources, Writing – review & editing. **BPIB**: Project administration, Funding acquisition.

ETHICS STATEMENT

This study was reviewed by the University of the Philippines Manila Research Ethics Board (UPMREB) Review Panel 2 and was granted exemption from ethical review. The exemption was issued under the code UPMREB 2023-0388-EX, with the date of action on 31 May 2023. The study qualified for exemption because it did not involve human participants, identifiable human tissue, biological samples, or individual

identifiable data, and therefore did not constitute human health research.

REFERENCES

al Hanbali, O. A., Khan, H. M. S., Sarfraz, M., Arafat, M., Ijaz, S., & Hameed, A. (2019). Transdermal patches: Design and current approaches to painless drug delivery. *Acta Pharmaceutica*, 69(2), 197-215. https://doi.org/10.2478/acph-2019-0016

Alcântara, M. T. S., Brant, A. J. C., Giannini, D. R., Pessoa, J. O. C. P., Andrade, A. B., Riella, H. G., & et al. (2012). Influence of dissolution processing of PVA blends on the characteristics of their hydrogels synthesized by radiation-Part I: Gel fraction, swelling, and mechanical properties. *Radiation Physics and Chemistry*, 81(9), 1465-1470.https://doi.org/10.1016/j.radphyschem.2012.01.048

Ananthu, L., & Vijetha, A. (2022). Formulation and evaluation of simvastatin transdermal drug delivery system. Saudi *Journal of Medical and Pharmaceutical Sciences*, 8(10), 527-535. https://doi.org/10.36348/sjmps.2022.v08i10.006

Anod, H. V., Gupta, N. V., Gowda, D. V., & Manohar, M. (2018). Preparation and evaluation of simvastatin transdermal film. *International Journal of Applied Pharmaceutics*, 10(5), 235-238. https://doi.org/10.22159/ijap.2018v10i5.26657

Cherukuri, S., Batchu, U., Mandava, K., Cherukuri, V., & Ganapuram, K. (2017). Formulation and evaluation of transdermal drug delivery of topiramate. *International Journal of Pharmaceutical Investigation*, 7(1), 10-17. https://doi.org/10.4103/jphi.JPHI_35_16

Das, S., Sarkar, P., & Majee, S. B. (2022). Polymers in matrix type transdermal patch. *International Journal of Pharmaceutical Sciences Review and Research*, 73(1), 77-86. https://doi.org/10.47583/ijpsrr.2022.v73i01.014

Dash, S., Murthy, P. N., Nath, L., & Chowdhury, P. (2010). Kinetic modeling on drug release from controlled drug delivery systems. *Acta Poloniae Pharmaceutica*, 67(3), 217-223.

El-Say, K. M., Ahmed, O. A. A., Aljaeid, B. M., & Zidan, A. S. (2015). Matrix-type transdermal films to enhance simvastatin ex vivo skin permeability. *Pharmaceutical Development and Technology*, 22(4), 492-499. https://doi.org/10.3109/10837450.2015.1102279

França, M. T., Mendes, C., Silva, A. H., Valentini, G., Cisilotto, J., Parize, A. L., & et al. (2022). Blended polymeric films containing the drugs simvastatin and resveratrol: The supersaturation approach for melanoma treatment. *Colloids and Interface Science Communications*, 46, Article 100501. https://doi.org/10.1016/j.colcom.2021.100501

Fu, Y., & Kao, W. J. (2010). Drug release kinetics and transport mechanisms of non-degradable and degradable polymeric delivery systems. *Expert Opinion on Drug Delivery*, 7(4), 429-444. https://doi.org/10.1517/17425241003602259

Haq, A., Goodyear, B., Ameen, D., Joshi, V., & Michniak-Kohn, B. (2018). Strat-M® synthetic membrane: Permeability comparison to human cadaver skin. *International Journal of Pharmaceutics*, 547, 432-437. https://doi.org/10.1016/j.ijpharm.2018.06.012

Hossain, M. K., Subedi, R. K., Chun, M. K., Kim, E. J., Moon, H. S., & Choi, H. K. (2011). Formulation and in vitro evaluation of transdermal drug delivery system for galantamine. *Journal of Pharmaceutical Investigation*, 41(1), 1-7. https://doi.org/10.4333/KPS.2011.41.1.001

Idrees, A., Rahman, N. U., Javaid, Z., Kashif, M., Aslam, I., Abbas, K., & et al. (2014). In vitro evaluation of transdermal patches of flurbiprofen with ethyl cellulose. *Acta Poloniae Pharmaceutica*, 71(2), 287-295.

Kandavilli, S., Nair, V., & Panchagnula, R. (2002). Polymers in transdermal drug delivery systems. *Pharmaceutical Technology*, 26, 62-80.

Korani, S., Bahrami, S., Korani, M., Banach, M., Johnston, T. P., & Sahebkar, A. (2019). Parenteral systems for statin

delivery: A review. *Lipids in Health and Disease,* 18(1), 193-201.https://doi.org/10.1186/s12944-019-1139-8

Krishnam Raju, K., Sudhakar, B., & Murthy, K. V. R. (2014). Factorial design studies and biopharmaceutical evaluation of simvastatin loaded solid lipid nanoparticles for improving the oral bioavailability. *ISRN Nanotechnology*, 2014, Article 478965.https://doi.org/10.1155/2014/951016

Latif, M. S., Azad, A. K., Nawaz, A., Rashid, S. A., Rahman, M. H., Al Omar, S. Y., & et al. (2021). Ethyl cellulose and hydroxypropyl methyl cellulose blended methotrexate-loaded transdermal patches: In chemico and ex vivo. *Polymers*, 13(20), Article 3455. https://doi.org/10.3390/polym13203455

Madgulkar, A., Bhalekar, M., More, S., & Pardeshi, S. (2020). Formulation, optimization and evaluation of simvastatin buccal patch for local treatment of periodontitis. *World Journal of Pharmaceutical Research*, 9(5), 1046-1061.

Manalo-Cabalinan, R. A. M., & Bulatao, B. P. I. (2026). Impact of varied polymer ratios on the physicochemical characteristics and release profiles of a matrix-type transdermal patch of simvastatin. *SciEnggJ*, 19(1), 89-97.

Manalo-Cabalinan, R. A. M., Cueva, J. P. T., & Bulatao, B. P. I. (n.d.). Bulk formulation of matrix-type simvastatin transdermal patch and analysis of simvastatin content using high-performance liquid chromatography [Unpublished invention disclosure form].

Mehdizadeh, A., Toliate, T., Rouini, M., Abashzadeh, S., & Dorkoosh, F. (2004). Design and in vitro evaluation of new drug-in-adhesive formulations of fentanyl transdermal patches. *Acta Pharmaceutica*, 54(4), 301-317.

Parhi, R., & Padilam, S. (2018). In chemico permeation and stability studies on developed drug-in-adhesive transdermal patch of simvastatin. Bulletin of Faculty of Pharmacy, Cairo University, 56(1), 26-33. https://doi.org/10.1016/j.bfopcu.2018.04.001

Parhi, R., & Suresh, P. (2016). Formulation optimization and characterization of transdermal film of simvastatin by response surface methodology. *Materials Science and Engineering: C*, 58, 331-341. https://doi.org/10.1016/j.msec.2015.08.056

Pastore, M. N., Kalia, Y. N., Horstmann, M., & Roberts, M. S. (2015). Transdermal patches: History, development and pharmacology. *British Journal of Pharmacology*, 172(9), 2179-2209. https://doi.org/10.1111/bph.13059

Patel, D. P., Setty, C. M., Mistry, G. N., Patel, S. L., Patel, T. J., Mistry, P. C., & et al. (2009). Development and evaluation of ethyl cellulose-based transdermal films of furosemide for improved in chemico skin permeation. *AAPS PharmSciTech*, 10(2), 437-442. https://doi.org/10.1208/s12249-009-9224-3

Rastogi, V., & Yadav, P. (2012). Transdermal drug delivery system: An overview. *Asian Journal of Pharmaceutics*, 6(3), 161-170. https://doi.org/10.4103/0973-8398.104828

Sabbagh, F., & Kim, B. S. (2022). Recent advances in polymeric transdermal drug delivery systems. *Journal of Controlled Release*, 341, 132-146. https://doi.org/10.1016/j.jconrel.2021.11.025

Shabbir, M., Ali, S., Raza, M., Sharif, A., Akhtar, M. F., Manan, A., & et al. (2017). Effect of hydrophilic and hydrophobic polymer on in chemico dissolution and permeation of bisoprolol fumarate through transdermal patch. *Acta Poloniae Pharmaceutica*, 74(1), 187-197.

Siepmann, J., & Siepmann, F. (2008). Mathematical modeling of drug delivery. *International Journal of Pharmaceutics*, 364(2), 328-343. https://doi.org/10.1016/j.ijpharm.2008.09.004

Uchida, T., Kadhum, W. R., Kanai, S., Todo, H., Oshizaka, T., & Sugibayashi, K. (2015). Prediction of skin permeation by chemical compounds using the artificial membrane, Strat-M™. *European Journal of Pharmaceutical Sciences*, 67, 113-118. https://doi.org/10.1016/j.ejps.2014.11.002

United States Pharmacopeial Convention. (2023). General chapter <3> topical and transdermal drug products-product quality tests. In United States Pharmacopeia and National Formulary (USP-NF). https://www.uspnf.com

Ward, N. C., Watts, G. F., & Eckel, R. H. (2019). Statin toxicity: Mechanistic insights and clinical implications. *Circulation Research*, 124(2), 328-350. https://doi.org/10.1161/CIRCRESAHA.118.312782

Wokovich, A. M., Strasinger, C., Kessler, J., Cai, B., Westenberger, B., Rhee, M. J., & et al. (2015). Cold flow

measurement of transdermal drug delivery systems (TDDS). *International Journal of Adhesion and Adhesives*, 59, 71-76. https://doi.org/10.1016/j.ijadhadh.2015.02.002

Zhang, Y., Huo, M., Zhou, J., Zou, A., Li, W., Yao, C., & et al. (2010). DDSolver: An add-in program for modeling and comparison of drug dissolution profiles. *The AAPS Journal*, 12(3), 263-271. https://doi.org/10.1208/s12248-010-9185-1