ARTICLE

Impact of varied polymer ratios on the physicochemical characteristics and release profiles of a matrix-type transdermal patch of simvastatin

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ABSTRACT

Simvastatin's (SMV) physicochemical properties, such as poor aqueous solubility and low bioavailability (< 5%), limit its biomedical applications. Transdermal delivery is one of the viable options that can improve its clinical use. This study aimed to evaluate the effect of varying the ratios of polyvinyl alcohol (PVA) and hydroxypropyl cellulose (HPC) on the physicochemical characteristics and release behavior of an SMV-loaded matrix-type transdermal patch. The developed patch was a binary matrix system, with an acrylate polymer providing adhesive properties and PVA alone as a backing membrane. The patches were then characterized in terms of SMV content, thickness, weight, moisture content, and folding endurance. The results demonstrated consistent SMV content and minimal variation in thickness and weight across formulations, indicating formulation uniformity. Polymer composition significantly influenced mechanical integrity and drug release behavior. Among the formulations evaluated, F1, with PVA/HPC ratio of 85:15, exhibited favorable physicochemical properties, controlled early-stage release, and a reproducible release rate consistent with sustained-release behavior. The study demonstrates that appropriate balancing of PVA and HPC in a binary matrix system enables controlled in vitro release of SMV and yields transdermal patches with acceptable formulation quality, providing a foundation for further optimization and transdermal performance evaluation including pharmacokinetic profile and drug permeation using *in vivo* studies.

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INTRODUCTION

Ischemic heart disease (IHD) remains the leading cause of mortality in the Philippines, accounting for 19.2% deaths in 2024 (Mapa 2025). A major contributing factor to IHD is hypercholesterolemia or increased blood cholesterol (Pirillo and Norata 2023). The commonly used drug prescribed to lower blood cholesterol is SMV (El-Say et. al, 2015). It is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, SMV, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form (Murtaza, 2012). SMV is available as immediate release tablets of different strengths (10–40 mg). Its bioavailability is estimated at only 5% after oral administration due to extensive hepatic first-pass metabolism and limited dissolution rate. Moreover, it is characterized by a low molecular weight of 418.56 Da, high lipid solubility, low melting point of 129°C and effectiveness in low plasma concentration (El-Say et. al, 2015).

Given the low bioavailability and limited dissolution rate of existing simvastatin dosage forms, an alternative formulation was previously explored in the form of simvastatin (SMV) transdermal patches using hydroxypropyl cellulose (HPC) as a single-polymer matrix (Bulatao et al., unpublished). This approach offered a promising alternative to conventional oral therapy by enabling ease of administration, controlled drug release, and bypass of hepatic first-pass metabolism, potentially reducing dosing frequency and systemic side effects.

However, despite preliminary pre-formulation efforts, formulation-level challenges were encountered. *In vitro* dissolution and skin permeation studies of the HPC-based transdermal patch

KEYWORDS

transdermal system, matrix-type, hydroxypropyl cellulose, polyvinyl alcohol, simvastatin

showed inconsistent and difficult-to-control release behavior (Bulatao et al., unpublished), indicating limitations in using a single-polymer matrix for a poorly water-soluble drug such as SMV. In addition, challenges related to matrix handling and formulation robustness became evident during preparation, particularly when transitioning from small-scale trial batches to bulk formulation.

In small-scale experiments, transdermal patches are typically prepared using small vessels such as beakers, which can mask formulation inefficiencies, including material loss, matrix heterogeneity, and variability in drug distribution. These limitations may lead to an overestimation of formulation robustness and underestimation of resource requirements during early development. Recognizing these challenges, further refinement of the formulation strategy was deemed necessary.

To address these formulation-level challenges, the present study explored the use of a binary polymer matrix system by combining HPC with polyvinyl alcohol (PVA), an amphiphilic polymer known for its film-forming ability, mechanical strength, and capacity to modulate drug release. The amphiphilic nature of such polymeric matrices facilitates improved drug distribution, wettability, and controlled release behavior in transdermal delivery systems (Cardona et al., 2024). Accordingly, this study aimed to systematically evaluate the effect of varying PVA–HPC ratios on the physicochemical properties and *in vitro* release profiles of a matrix-type SMV transdermal patch.

MATERIALS AND METHODS

Materials

Synthetic polymers, hydroxypropyl cellulose (Tokyo Chemical Industries Inc.) and polyvinyl alcohol (Tokyo Chemical Industries Inc.), served as drug reservoirs. Glycerin (Loba Chemicals), butylated hydroxytoluene (BHT, Sigma Aldrich), and acrylate polymer (Laguna, Philippines) were used as plasticizer, antioxidant, and adhesive, respectively. Phosphate-buffered saline (pH 7.4) was prepared using chemicals of analytical grade. SMV, which served as the active ingredient of the transdermal patch, was locally procured (MDLD Interchemical Industries Inc.).

Preparation of backing membrane

Different concentrations (5, 6, 7, and 8 % w/v) of PVA in distilled water were prepared. The solution was heated and mixed for 30 min at 130 °C and 6 rpm, and cooled for 10 min. A volume of 15 to 17 mL backing membrane solution (depending on the diameter of the petri dish) was poured into glass and plastic Petri dishes lined with wax. The backing membrane was air-dried for 2 days. The thickness of the prepared backing membrane was measured using a digital micrometer (Mitutoyo IP65 Coolant Proof Digimatic Micrometer, Japan).

Preparation of SMV transdermal patch

Polymer blends of HPC and PVA at varying ratios were prepared via solvent evaporation technique (Table 1). PVA was dissolved in 7.5 mL 80% (v/v) dimethyl sulfoxide in water and stirred at 80°C until the solution was clear. HPC was added slowly and continuously stirred until a homogenous solution was formed. Next, a 0.18 g BHT in 1.8 mL ethanol was added dropwise followed by the dropwise addition of 0.81 mL glycerin with 3 min of mixing for every addition of the reagents. A 0.3 mL acrylate polymer was added and stirred for 10 min to ensure homogeneity and then cooled to 50 °C.

Table 1: PVA and HPC ratio of each SMV transdermal patch formulation, n=3.

Formulation	PVA/HPC ratio	Weight of PVA, mg	Weight of HPC, mg
F1	85:15	688.5	121.5
F2	70:30	567	243
F3	60:40	486	324
F4	40:60	324	486
F5	30:70	243	567
F6	15:85	121.5	688.5
Pure HPC	100	-	810

Two grams of the prepared matrix solution, along with an additional 10% excess to compensate for potential excipient loss during the pouring process, was weighed and transferred to a clean beaker to formulate a 2 g patch. The solution was incrementally added with 1% (w/v) SMV in ethanol followed by a 3 min mixing period at 50 °C and pouring of the solution onto the previously prepared backing membrane using a glass mold (internal diameter: 4.7 cm × height: 1 cm). The ratio between the patch formulation and simvastatin was 2g : 10mg. An SMV-unloaded patch formulation was likewise prepared employing the same procedure, wherein the SMV solution was substituted with an equivalent volume of ethanol.

Characterization of the transdermal patches

The methods for characterizing the transdermal system were adapted from previous work (Latif et al. 2021; Prabhu et al. 2011; Shirisha et al. 2017) with modifications. The formulations were visually inspected for their color, clarity, flexibility, smoothness, and homogeneity.

SMV content

To determine the content of SMV in each patch, an accurately weighed 12.5 mg SMV standard was dissolved in 25 mL diluent (acetonitrile/0.3 % glacial acetic acid, pH 4, 8:2). A 5 mL aliquot was transferred in a 50 mL volumetric flask and diluted with diluent (intermediate standard solution). Different aliquots of the intermediate standard solution were transferred in a 10 mL volumetric flask containing 0.25 mL of the placebo formulation solution and diluted with diluent to produce a calibration curve (0.001 - 0.005 mg/mL). The standard curve was used to compute the SMV content (r^2: 0.9918 -0.9995) from the saturation solubility and formulation studies. The highest concentration was used for the system suitability. The prepared formulation was dissolved in 80% (v/v) ethanol, vortex mixed for 5 min, sonicated for 15 min, and vortex mixed for another 5 min. The flasks were diluted to volume with the diluent. The chromatographic parameters for the determination of SMV content in the transdermal system were as follows: mobile phase - acetonitrile/0.43% NaH_2PO_4 (65:35); detector of UV 238 nm; column: 4.6 mm × 150 mm C18 5 µm; column temperature of 45°C; flow rate of 1.5 mL/min; and injection volume of 10 µL (United States Pharmacopeia 43, 2019). All the solutions were filtered using a 0.45 µm syringe filter before

injection in the high-performance liquid chromatograph (Waters Alliance e2695).

Thickness
Thickness is a property which affects drug permeation in a transdermal system. It was measured using a digital micrometer (Mitutoyo IP65 Coolant Proof Digimatic Micrometer, Japan) at five different parts of the patch. The relative standard deviation (RSD) of the patch should be less than 5% to ensure uniformity (Ananda et al., 2021).

Average weight
Average weight is an important parameter influencing the release of the drug at a controlled and sustained rate, necessary for the effectiveness of the formulation. It was computed by individually weighing the transdermal system. The RSD should be less than 5% (Ananda et al., 2021).

Moisture content
Moisture content (%) ensures stability of the transdermal patch formulation and proper adhesion to the skin. It was determined by weighing the transdermal patches and storing them in a desiccator containing desiccant (activated silica) at room temperature for 24 h using Eq. 1 (Kim and Choi, 2021).

$$\% \text{ Moisture content} = \frac{\text{(Initial – final) patch weight}}{\text{Initial patch weight}} \times 100 \quad \text{Eq. 1}$$

Percent moisture uptake
The percent moisture uptake is crucial in maintaining the hydration and functionality of the transdermal patch (Chandan et al., 2022). It was determined by weighing the transdermal patches and storing them in a desiccator containing a 100 mL of saturated solution of aluminum chloride. The patches were taken out and weighed after 3 days. The percentage moisture uptake was calculated using Eq. 2.

$$\% \text{ Moisture uptake} = \frac{\text{(Initial – final) patch weight}}{\text{Initial patch weight}} \times 100 \quad \text{Eq. 2}$$

Folding endurance
Folding endurance is a critical property as it determines the ability of a transdermal patch to withstand frequent conditions of folding. It was measured as the number of times the film could be folded repeatedly at the same place without breaking or cracking (Malaiya et al., 2018).

Evaluation of the release profile
In vitro release
The experimental conditions for evaluating the release profile of SMV from the transdermal patches were adapted from a previously described literature (Altun et al. 2021) with modifications. For this study, a USP Dissolution Apparatus 5 (Hanson, Teledyne LABS, CA, USA) was used. PBS (pH 7.4) containing 0.5% (w/v) sodium lauryl sulfate (SLS) was used as the release medium to maintain sink conditions for simvastatin, a poorly water-soluble drug, and to prevent precipitation during extended-release testing. The concentration of SLS was selected to ensure reliable quantification of drug release while enabling comparison of release behavior among formulations with different polymer ratios. A patch was placed in each of the six vessels containing 900 mL of release medium, previously heated and maintained at 32°C. The release study was carried out at 50 rpm and a 10 mL sample was withdrawn from each vessel at 0.25, 0.5, 1, 2, 4, 8, 12, 24, 48, 72, and 96 h and replaced with 10 mL of previously heated release medium. The samples were filtered using a 0.45 µm nylon filter. The amount of SMV was quantified at 238 nm using a high-performance liquid chromatograph (Waters Alliance e2695) and interpolated using the calibration curve. The cumulative amount of SMV (%) was determined based on Eq. 3 (Song et al., 2014):

$$\% \text{ CR} = \frac{V_e \sum_{i=1}^{n-1} C_{n-1} + V_o C_n}{m} \times 100 \quad \text{Eq. 3}$$

where CR is the cumulative amount of SMV released (%), V_e is the sampled volume (10 mL), V_o is the volume of release medium (900 mL), C_n is the concentration at the particular time point (mg/mL), and m is the initial amount of SMV in the patch (mg).

Release kinetics modelling
The release data were fitted in different mathematical models (Zero order, First order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell) to describe the release behavior of SMV from the matrix patch using DDSolver. The best-fitted model was selected based on the highest coefficient of determination, r^2 (Latif et al. 2022).

Statistical analysis
All quantitative data were reported as mean ± standard deviation from at least three independent experiments using GraphPad Prism 9.3.0 (San Diego, CA, USA). Normality was tested using Shapiro-Wilk test. For comparison of different groups, a one-way analysis of variance followed by Tukey's post hoc test were performed. A p-value of less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Preparation of the backing membrane
The backing membrane was prepared using PVA in water at different concentrations: 5, 6, 7, and 8 % (w/v) in both glass and plastic Petri dishes as molds. Negligible differences in the thickness between plastic and glass molds were observed across all concentrations (Figure 1). This indicates the type of molding did not affect the backing membrane's thickness.

For glass alone, there was a significant difference between 5% and 8% PVA (p=0.0153) while for plastic alone, no statistically significant difference was observed. It was concluded that 7% PVA in water in a glass mold appeared to be the most suitable condition because it showed characteristic thickness between 0.122 to 0.219 mm, similar with commercially available backing membrane (3M Medical Materials & Technologies 2022) and can be folded numerous times without breaking.

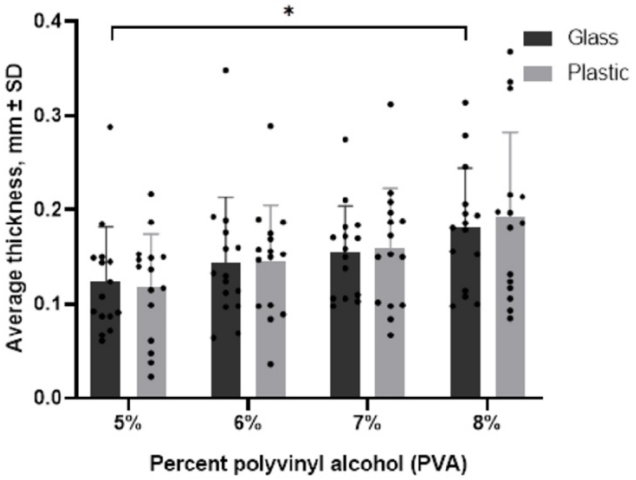

Figure 1: Varying percentages of PVA did not show any significant differences in the thickness of the backing membrane. The material used to mold the backing membrane did not also affect the thickness of the produced backing membrane. *p<0.05 (n=12).

Characteristics of the formulated patch
Figure 2 shows F1 to F6 and pure HPC formulations. All formulations displayed clear, transparent, and smooth appearance.

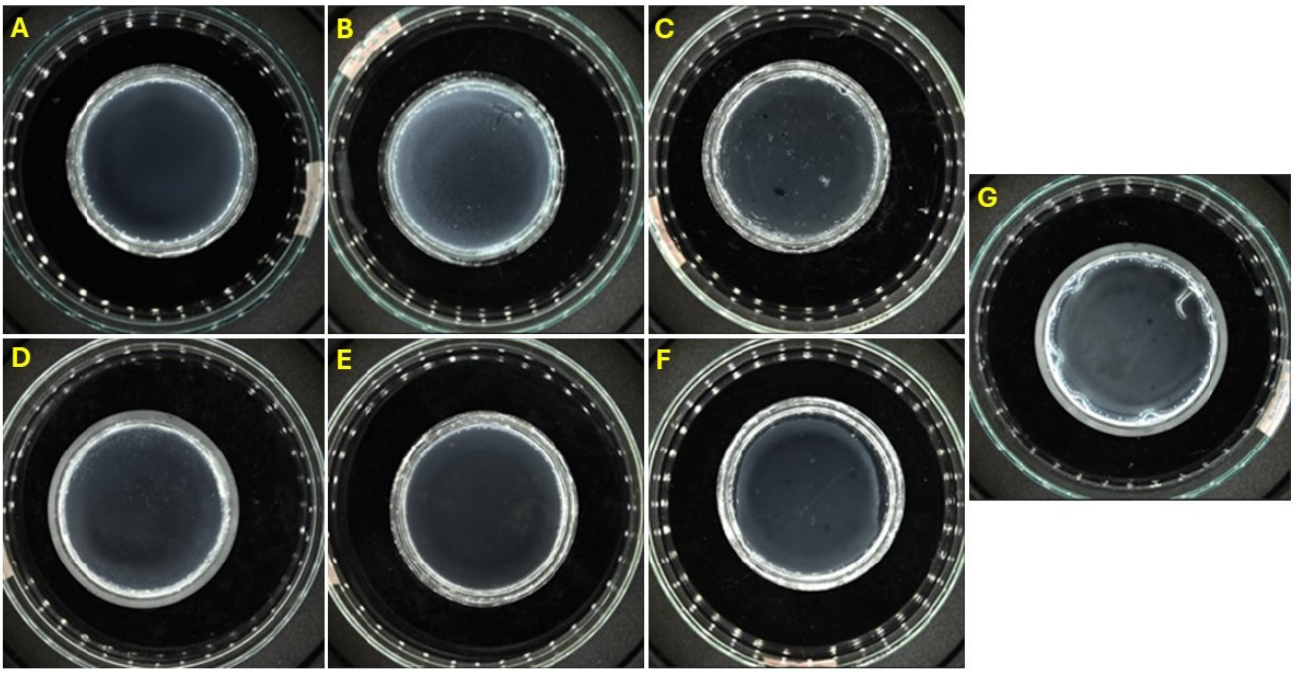

Figure 2: Representative SMV matrix-type formulations. A. F1 (85:15 PVA/HPC), B. F2 (70:30 PVA/HPC), C. F3 (60:40 PVA/HPC), D. F4 (40:60 PVA/HPC), E. F5 (30:70 PVA/HPC), F. F6 (15:85 PVA/HPC), G. Pure HPC (100 HPC).

Assay was done using HPLC to determine the content of SMV incorporated in the patch formulations. A consistent SMV content of 60 to 74% was obtained for all the formulations (Table 2). The relatively low percent assay was due to the hardened formulation that remained in the beaker during pouring, accounting for 30 to 40% of the SMV. Hence, pouring in molds should be done while the formulation is warm. However, this also affected the weight of the formulation (and SMV amount) once cooled, as hot samples will give erroneously lower weight readings due to convective currents that affect the balance mechanism (Dmitriev et al. 2003).

Table 2: Characterization of SMV matrix-type transdermal patch (F1 to F6, pure HPC, n= 3).

Formulation code	Characteristics					
	Assay (%)	Thickness (mm)	Weight (g)	Moisture (%)	Moisture uptake (%)	Folding endurance (folds)
F1	71.75 ± 0.49	0.25 ± 0.03	2.91 ± 0.12	0.30 ± 0.06	0.28 ± 0.01	>500
F2	77.00 ± 3.53	0.26 ± 0.01	2.94 ± 0.14	0.28 ± 0.02	0.27 ± 0.01	>500
F3	64.77 ± 1.90	0.24 ± 0.00	2.98 ± 0.07	0.22 ± 0.07	0.18 ± 0.02	>500
F4	60.07 ± 1.44	0.17 ± 0.05	2.89 ± 0.12	0.11 ± 0.01	0.19 ± 0.02	252.67 ± 6.43
F5	68.22 ± 2.61	0.14 ± 0.02	2.79 ± 0.09	0.31 ± 0.06	0.17 ± 0.05	31.33 ± 2.31
F6	74.38 ± 0.72	0.16 ± 0.00	2.79 ± 0.10	0.27 ± 0.06	0.20 ± 0.02	8.00 ± 2.00
Pure HPC	61.11 ± 2.93	0.16 ± 0.01	2.82 ± 0.10	0.22 ± 0.04	0.18 ± 0.04	4.00 ± 0.00

The thickness of the samples ranges from 0.16 ± 0.00 - 0.26 ± 0.01 mm. Their weight varied between 2.79 ± 0.09 to 2.98 ± 0.07 g. Both thickness and weight showed minimal variation as seen by the low standard deviation values. These findings indicate that the protocols used for the patch preparation were reproducible (Singh and Bali, 2016). Collectively, the consistency in assay values, dimensional uniformity, controlled moisture behavior, and folding endurance supports the pharmaceutical elegance of the prepared patches, reflecting acceptable formulation quality and handling characteristics.

To assess the stability of the prepared patches under ambient conditions, moisture content was investigated. The moisture levels of the prepared patches ranged from 0.11 ± 0.01 to 0.31 ± 0.06%. The low moisture values of the patches can be equated to their stability, as low moisture helps prevent drying and subsequent brittleness during long- term storage at ambient temperatures (Mutalik and Udupa 2004). Moreover, low moisture absorption of the patches, varying from 0.18 ± 0.02 to 0.28 ± 0.01%, was observed which demonstrates their integrity in humid conditions. The low moisture protects the patches against microbial growth and contamination (Shirisha et al. 2017; Singh and Bali 2016), thereby maintaining overall quality and pharmaceutical elegance.

Folding endurance is an important measure of the mechanical strength of the patches, which is essential in ensuring integrity of the product during handling, storage, and application (Soral et al. 2021). An increasing folding endurance was observed with increasing concentration of PVA. Particularly, F5, F6, and pure HPC showed significantly lowered folding endurance values, indicating weak and less durable formulation compared with F1 to F4. This observation is supported by the ability of the PVA to improve mechanical properties (tensile strength and tensile modulus) when blended with HPC polymer (El-Hag et al. 2017). Hence, only F1 to F4 were further tested for the SMV release profile.

Release profiling of SMV from the patches

Saturation solubility

The saturation solubility of SMV in pH 7.0 buffer was reported to be 24.4 µg/mL (Rao et al. 2010). This value was the basis for choosing the volume of the release medium (900 mL) in the release study. This infinite volume ensures that the SMV released from the patch does not precipitate in the medium while performing the experiments, leading to its accurate measurement. A conventional USP buffer was used, PBS (pH 7.4) with 0.5 % (w/v) SLS, for technical simplicity reasons (Niederquell et al. 2023).

In vitro release

The release study was designed to evaluate the discriminatory power of the method in distinguishing formulation-dependent release behavior, rather than to simulate *in vivo* skin permeation. The USP Apparatus 5 was used, consisting of a watch glass-patch-Teflon™ mesh sandwich assembly coupled with the USP Apparatus 2 or paddle method. A similar study used this apparatus to assess the drug release characteristics during the early development phase of the transdermal patch (Costa and Sousa Lobo 2003). It is essential to evaluate the release profile of a transdermal patch for several days to understand if the patch can sustain the delivery of SMV for a prolonged period, simulating the performance of transdermal patches in the clinic. This measure is crucial for drug delivery systems for sustaining therapeutic efficacy, possibly preventing side effects, and avoiding frequent administration (Altun et al. 2021).

As shown in Table 3 and Figure 3, a faster release was observed in all formulations within 12 h. At the end of the 96-h release study, F1, F3, and F4 released at least 85% of SMV, demonstrating that majority of SMV had been released (European Medicines Agency 2014). However, there was no clear trend on the effects of varying the ratio of PVA and HPC by just observing their general release profiles.

Table 3: Release profile of the SMV from the fabricated transdermal patches, n = 6.

Time (h)	Release (%)							
	F1		F2		F3		F4	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0.25	6.23	1.68	18.47	2.25	16.82	8.93	1.58	0.57
0.5	10.22	2.07	31.41	5.12	29.17	10.08	2.42	0.62
1	15.49	6.52	47.42	6.19	41.64	12.24	10.18	2.88
2	32.08	10.02	64.78	8.08	57.05	9.22	25.68	5.43
4	51.20	7.96	75.97	8.68	61.74	10.91	45.70	10.68
8	61.07	7.04	84.95	6.55	73.55	10.62	74.06	4.89
10	74.89	6.41	90.73	3.48	87.41	6.13	83.34	1.70
24	84.17	7.00	93.87	4.47	95.84	2.90	93.78	2.81
48	90.65	3.16	87.45	5.26	94.22	3.47	91.48	4.65
72	90.06	5.06	80.60	4.98	94.66	3.86	88.81	3.01
96	87.91	5.65	80.42	6.12	94.60	3.87	89.35	3.57

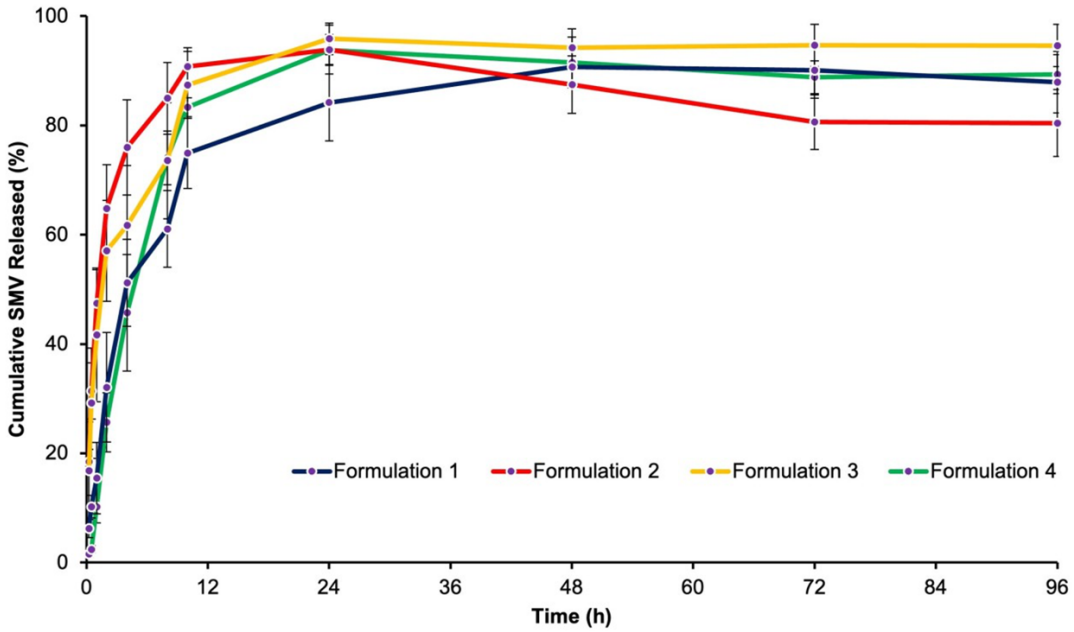

Figure 3: Cumulative release of SMV from the fabricated transdermal patches.

Next, we evaluated selected sampling time points to differentiate the release behavior of the four formulations, focusing on (a) early-stage release (approximately 20–30% SMV released), which may indicate an initial burst release; (b) mid-stage release (approximately 50%), reflecting the overall shape of the release profile; and (c) late-stage release (>85%), indicating the extent of drug release. F2 and F3 released about 30% of SMV within 30 min and more than 40% of SMV within 1 h. In orally administered SMV drug products, the maximum concentration of SMV in the blood was reported to occur after 2.4 h (Ellison et al. 1993). For transdermally administered drugs, these results may indicate an initial burst release. However, F1 and F4 exhibited a steady increase and releasing a rather low quantity of SMV (less than 20% of SMV) within 1 h. These findings may be attributed to the design of the transdermal patch as it is heavily influenced by formulation components (Wang et al. 2023). Among the 4 formulations, F1 had the highest PVA and lowest HPC contents while F4 had the lowest PVA and highest HPC contents. Therefore, adjusting the component ratios of PVA and HPC influenced the release profiles. It must be noted that both PVA and HPC are amphiphiles that control the release of drugs through certain degrees of hydrophobicity and hydrophilicity (Zuppolini et al. 2022). They increase wettability and solubility of poorly soluble drugs (Rashid et al. 2015). Hence, F1 and F4 were able to prevent the initial burst release of SMV. The burst effect happens when the skin is saturated with the drug, leading to a spike in the concentration of the drug in the blood followed by a decline to a steady value. This effect is undesirable as the concentration of the drug exceeds its toxicity limit (Nauman et al. 2011). About half of SMV was released within 1.5 h for F2 and F3 while 4 h for both F1 and F4. Lastly, about 85% of SMV were released from F2, F3, and F4 within 8 to 10 h. Remarkably, about 85% of SMV were released from F1 in 24 h was observed.

The plateau that can be observed in F1, F3, and F4 further differentiates these formulations, indicating their controlled-release behavior. Evidently, F2 reached a maximum cumulative release at 24 h, after which minor fluctuations were observed at later time points. These variations are attributed to experimental variability inherent to extended *in vitro* release testing and do not indicate a true decrease in cumulative drug release. Minor variability in cumulative release values at extended time points may arise from repeated sampling, medium replacement, and analytical variability, which is inherent to long-duration *in vitro* release studies. The subtle differences among the 4 formulations could probably be due to the presence of, and not due to the ratios of, PVA and HPC. The PVA served to distribute the SMV molecules uniformly in the patches, ensuring the retention of the amorphous state of SMV. Drug molecules that are close to each other may cause supersaturation, leading back to their crystalline equilibrium solubility (Brough et al. 2016). It can be speculated that the effects of heating on the formulation components during the preparation were insignificant due to the high glass transition temperature (Tg) and melting point (Tm) of PVA. Both high Tg and Tm resulted in lower molecular mobility and thus, higher stability of SMV-in-polymer matrix. This stability can immobilize SMV molecules, preventing their recrystallization (Zuppolini et al. 2022). Retention of the amorphous state is important as it ensures even distribution of SMV within the matrix and a controlled-release profile. Moreover, a low molecular weight PVA (Brough et al. 2016) and HPC (Martin-Pastor and Stoyanov 2021) were used due to their advantages of preventing drug precipitation and solubilizing non-polar drugs such as SMV, respectively. All formulations also released more than 85% of SMV, signifying the importance of a binary matrix system for SMV.

The release behavior of SMV from the matrix-type patches is strongly influenced by the physicochemical properties of the polymeric excipients used. PVA is an amphiphilic polymer capable of interacting with hydrophobic drug molecules while simultaneously undergoing hydration and swelling in aqueous environments. This dual behavior facilitates uniform drug distribution within the matrix and contributes to diffusion-controlled release. HPC, on the other hand, acts as a hydrophilic swellable polymer that increases matrix hydration, enhances wettability, and promotes drug diffusion through the hydrated polymer network. The combination of PVA and HPC in a binary matrix system allows modulation of matrix porosity, hydration rate, and polymer chain mobility, which collectively govern the release kinetics of simvastatin. Although the present study did not directly evaluate skin permeation, these polymer properties are also relevant to transdermal delivery, as polymer hydration and drug partitioning from the matrix are key prerequisites for subsequent diffusion into the stratum corneum. In addition, PVA and cellulose-based polymers have been widely reported to be biocompatible and suitable for transdermal applications, with their amphiphilic nature supporting drug release while minimizing skin irritation.

The SMV release rates from the formulations based on the generated regression lines were also reported. The release rate of a drug from a patch is product-specific to assure batch-to-batch uniformity. This measure evaluates the reproducibility of the method in preparing the patches and is predictive of its capacity to be scaled up for producing the pilot and commercial batches. As shown in Table 4, one-way ANOVA revealed significant differences in the release rates of the 4 formulations ($p<0.0001$). The following trend can be observed: F4 > F1 > F3 > F2. Multiple comparison tests revealed statistically significant differences among the 4 formulations. The findings have not only demonstrated the reproducibility of the method in preparing the patches based on the insignificant standard deviation of the assay results but also the discriminatory power of the release profiling to detect differences in the components of the formulation e.g. varying ratio of PVA and HPC.

While Franz diffusion cell systems are more suitable for evaluating skin permeation and *in vivo* relevance, the present study focused on early-stage formulation screening and method discrimination. Future studies will incorporate skin-based permeation models, such as Franz diffusion cells, to further assess transdermal performance. Moreover, it will further elucidate the role of excipients in biological membrane interaction and transdermal drug delivery.

Table 4: Parameters of the SMV transdermal systems evaluated.

System	SMV content (mg)[a]	Surface area (cm^2)	Release rate (mg/h)[b]
F1	7.52 ± 0.35	19.64	0.0560 ± 0.0058
F2	7.89 ± 0.23	19.64	0.0271 ± 0.0071
F3	9.36 ± 0.08	19.64	0.0556 ± 0.0048
F4	8.67 ± 0.52	19.64	0.0678 ± 0.0067

[a] Based on the assay of 3 patches per formulation.

[b] Based on the evaluation of 6 patches per formulation (F1 vs F2, $p < 0.0001$; F1 vs F3, $p > 0.05$; F1 vs F4, $p = 0.031$; F2 vs F3, $p < 0.0001$; F2 vs F4, $p < 0.0001$; F3 vs F4, $p = 0.025$).

Kinetics of SMV release

Various mathematical release kinetic models were tested to describe the mechanisms involved in the release of SMV from the patches (Table 5). The coefficient of determination (r^2) was used as an indicator of best fitting. The model with the highest r^2 was considered the best-fitting model (Costa and Sousa Lobo 2003). F1, F2, and F3 fitted to the Korsmeyer-Peppas model, signifying that the patches were all Fickian diffusion- controlled type ($n<0.5$). This means that the drug release is controlled by diffusion of SMV through the matrix. F4 was predominantly following first order where the rate of drug release decreases exponentially over time. Molecular dynamic studies have shown that the non-polar parts of both SMV and PVA freely interact, promoting the solubility of SMV. There is also no cross-linking involved between SMV and PVA. Based on this previous study, it was shown that a zero-order release kinetics of SMV appears within the PVA matrix (Baptista et al. 2016). A binary matrix system of PVA and HPC would then offer a diffusion-controlled delivery system, offering a slow release of SMV, thus preventing side effects. Overall, the initial burst release effect was not observed in F1 and F4, but a sustained-release profile was observed in F1, F3, and F4. Moreover, F1 and F3 had stable release patterns and do not difer significantly in release rates ($p = 1.000$). Therefore, based on a qualitative and quantitative standpoint, F1, having the highest PVA and lowest HPC, can be further studied and optimized for a transdermal drug delivery system.

Table 5: Release kinetics of the patches fitted to various models.

System	Zero order		First order		Higuchi		Korsmeyer-Peppas			Hixson-Crowell	
	k_0	r^2	k_1	r^2	k_H	r^2	k_{KP}	n	r^2	r^2	k_{HC}
F1	0.983	–0.294	0.060	0.4309	9.914	0.578	22.415	0.272	0.8434	0.013	0.2576
F2	0.997	–3.7367	0.222	–0.4108	10.056	–1.3636	41.036	0.136	0.5933	0.015	–1.9662
F3	1.319	–1.9383	0.259	0.7577	12.721	–0.1939	42.488	0.188	0.8362	0.016	–0.3243
F4	1.156	–0.1599	0.118	0.8519	10.882	0.5667	25.281	0.285	0.7512	0.015	0.5722

The present study has several strengths. First, a systematic evaluation of polymer ratios in a binary matrix system was conducted, enabling direct comparison of formulation-dependent effects on physicochemical properties and in vitro release behavior of simvastatin. Second, the use of a compendial in vitro release testing apparatus (USP Apparatus 5) provided a standardized and reproducible platform to assess formulation discrimination and release kinetics. Third, consistent assay results and low variability in physicochemical parameters across replicate formulations indicate robustness of the laboratory-scale fabrication process.

However, several limitations can be acknowledged. The study focused on *in vitro* release testing and did not include skin permeation experiments using biological membranes, such as Franz diffusion cell studies, nor did it evaluate *in vivo* transdermal performance. As such, the release data cannot be directly extrapolated to predict skin permeation or clinical efficacy. In addition, the fabrication process was performed at laboratory scale, and further work is required to assess scalability, process validation, and long-term stability under storage conditions. Despite these limitations, the findings provide valuable insight into formulation design and identify practical working ranges for polymer ratios, serving as a foundation for subsequent optimization and translational studies.

CONCLUSION

Poor aqueous solubility and low bioavailability limit the therapeutic application of simvastatin, prompting the need for alternative delivery strategies such as transdermal systems. However, challenges related to formulation handling, matrix integrity, and controlled drug release must be addressed during early development. The present study aimed to investigate how varying ratios of polyvinyl alcohol (PVA) and hydroxypropyl cellulose (HPC) influence the physicochemical characteristics and *in vitro* release behavior of a matrix-type simvastatin transdermal patch.

To address these challenges, a series of transdermal patches containing different PVA–HPC ratios were prepared using a laboratory-scale solvent evaporation method and systematically characterized for assay, thickness, weight uniformity, moisture behavior, folding endurance, and *in vitro* drug release using a compendial release-testing apparatus. Comparative evaluation of the release profiles and release rates demonstrated that polymer composition significantly influenced release behavior and mechanical integrity. The prepared simvastatin matrix-type transdermal patches demonstrated characteristics consistent with pharmaceutical elegance, as evidenced by uniform drug content, minimal variation in thickness and weight, low moisture content and moisture uptake, and adequate folding endurance. These properties indicate formulation uniformity, mechanical robustness, and suitability for handling at the formulation development stage.

Among the formulations evaluated, F1 exhibited favorable physicochemical properties, controlled early-stage release behavior, and a reproducible release rate comparable to other sustained-release formulations, making it the most suitable formulation at the formulation-development stage. These findings indicate that appropriate balancing of PVA and HPC content is critical in achieving controlled release while maintaining patch integrity. Ultimately, this study demonstrates the feasibility of delivering simvastatin using a matrix-type transdermal patch and provides a formulation framework that may support further development of transdermal delivery systems for poorly soluble drugs.

Future studies should focus on further optimization of the selected formulation using systematic design approaches, evaluation of skin permeation using biological membrane models, assessment of long-term stability, and investigation of scalability to support translation toward transdermal drug delivery applications.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

CONTRIBUTIONS OF INDIVIDUAL AUTHORS

Richelle Ann M. Manalo-Cabalinan: Conceptualization and design of work, data gathering, acquisition, analysis and interpretation of data, writing – original draft. Bryan Paul I. Bulatao: Conceptualization and design of work, data gathering, acquisition, analysis and interpretation of data, writing – review and editing.

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