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RESEARCH ARTICLE
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# IN-VITRO FORMULATION AND EVALUATION OF SIMVASTATIN NANO SUSPENSION INCORPORATED TRANSDERMAL PATCH

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**ABATRACT**

**Objective**: The study aimed to develop Simvastatin-loaded transdermal films for the treatment of hyperlipidemia and to examine the effect of polymer concentration on drug penetration.

**Methods**: The transdermal films were prepared using the solvent evaporation method and evaluated for various physicochemical properties, including weight variation, thickness, drug content, moisture content, and folding endurance. Additionally, in vitro drug release studies and kinetic analyses were performed.

**Results**: By using Melvern zetasizer the particle size was found in the range between 964.7 nm and 130.8 nm. A formulation with lower size of 130.8 nm was selected for further studies, and its surface charge of zeta potential was negative. The SEM image shows that nanoparticles were within the nano range The prepared simvastatin nano suspension incorporated films were of uniform weight. Thickness varied from 230.4 to 307.95 µm. The drug content in all formulations ranged from 90.09% to 97.16%. Moisture content was between 3.71% and 6.89%, while moisture uptake varied from 5.56% to 8.22%. Folding endurance results were satisfactory, with the F3 formulation exhibiting the highest drug release.

**Conclusion**: The study concluded that among the many formulations tested, the F3 formulation was the best, with 90.2% drug release at 24 hours.

**Keywords:** Transdermal films, Simvastatin, Penetration enhancement, Solvent evaporation, Folding endurance

## INTRODUCTION

Transdermal films are an advanced drug delivery system designed to provide a continuous release of medication through the skin into the systemic circulation. They offer notable benefits, including maintaining steady drug levels in the blood, reducing the risk of side effects, enhancing bioavailability, and improving patient adherence to treatment [1]. As an alternative to oral administration, this approach prevents drug degradation caused by gastric pH and enzymatic activity, while also bypassing several steps of the metabolic pathway [2]. Simvastatin, an HMG-CoA reductase inhibitor, functions as an antihyperlipidemic agent and is a structural analogue of HMG-CoA [3]. HMG-CoA reductase facilitates the removal of about 70–75% of LDL through endocytosis. In the liver, cholesterol esters from LDL particles are broken down to release free cholesterol. The liver also produces cholesterol via de novo synthesis, a process that involves the formation of mevalonic acid catalyzed by the

enzyme HMG-CoA reductase [4]. Statins exert their therapeutic effect by inhibiting this rate-limiting enzyme, thereby reducing cholesterol production. This reduction stimulates the synthesis of high-affinity LDL receptors, enhancing the clearance of cholesterol-rich plasma LDL and consequently lowering plasma LDL cholesterol levels. At maximum doses, statins can decrease LDL concentrations by 30–50% [5]. Simvastatin is lipophilic and undergoes extensive first-pass metabolism, resulting in a plasma half-life of about 2 hours and an oral bioavailability of only 5% [6]. Transdermal, rectal, buccal, and parenteral delivery methods are among the innovative approaches employed to overcome this limitation [7]. Simvastatin is well-suited for transdermal film development due to its low molecular weight (418.56 g/mol), high lipid solubility, low melting point (129 °C), effectiveness at low plasma concentrations, and extensive first-pass metabolism [8]. The films were prepared using the solvent evaporation method, which involves dissolving the drug in a volatile solvent and then allowing the solvent to evaporate. This technique helps prevent thermal degradation of the drug, as organic solvents evaporate at relatively low temperatures [9]. Nano suspension is defined as drug particles dispersed in a continuous liquid phase and stabilized using surfactant agents. Pharmacological nanosuspension is a submicron sized drug particle, dispersed in an aqueous or non-aqueous vehicle, intended for oral, topical, injectable and pulmonary administration [10]. Drug particles in nanosuspension are usually less than 1μm in size, usually ranging from 200 nm to 600 nm [11]. Additionally, the use of nano suspension increases the formulation cost since the techniques used in preparation are more expensive. The aim of the current study was to create a cost-effective transdermal formulation that could release Simvastatin smoothly and sustainably.

## MATERIALS AND METHODS

The drug samples of Simvastatin (purity 98%, Macklin), Hydroxy propyl methylcellulose (Macklin), Eudragit RL-100 (Evonik), Dibutyl Phthalate (Sigma-Aldrich), Dimethyl sulpfoxide (Sangin biotech) and Poly vinyl alcohol (Sigma-Aldrich), were supplied by Biolution Resource, Malaysia. Every additional chemical utilized in the experiment was of analytical quality.

**Table 1: Composition of the transdermal patch**

| S,No. | Ingredients | Formulation | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 |
| **1** | **Simvastatin (mg)** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **2** | **Hydroxypropyl methyl cellulose (mg)** | 60 | 40 | 20 | 60 | 20 | 60 | 20 | 60 | 20 | 40 |
| **3** | **Eudragit RL 100 (mg)** | 50 | 30 | 10 | 50 | 10 | 10 | 50 | 10 | 50 | 30 |
| **4** | **Dimethyl sulfoxide (ml)** | 0.03 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.05 | 0.05 | 0.05 |
| **5** | **Dibutyl phthalate (ml)** | 0.02 | 0.03 | 0.02 | 0.02 | 0.04 | 0.02 | 0.04 | 0.02 | 0.02 | 0.04 |
| **6** | **Distilled water + Ethanol** | 1:1 | 1:1 | 1:1 | 1:1 | 1:1 | 1:1 | 1:1 | 1:1 | 1:1 | 1:1 |

## PREPARATION OF SIMVASTATIN NANO SUSPENSION

Accurately, 100 mg of Simvastatin and 10 mg of Sodium Lauryl Sulphate were dissolved in 100 ml of distilled water and shaken for 30 minutes using a magnetic stirrer. The prepared solution was then subjected to homogenization with different rpm and processing time and formulation by using WiseTis homogenizer and then sonicated for 10-20 min [12].

**Table 2: Homogenization cycles, homogenization and sonication time for the preparation of Simvastatin nano suspension**

| Run | Homogenization cycles | Homogenization time | Sonication time |
|---|---|---|---|
| | Minute | minute | minute |
| **1** | 9000 | 30 | 15 |
| **2** | 10000 | 20 | 15 |
| **3** | 8000 | 20 | 15 |
| **4** | 9000 | 20 | 20 |
| **5** | 10000 | 30 | 20 |

## PREPARATION OF SIMVASTATIN NANO SUSPENSION INCORPORATED MATRIX FILM

The process of solvent casting was applied in the preparation of the transdermal patch. To create the simvastatin nano suspension, first the polymer Eudragit RL-100 was dissolved in ethanol and then HPMC was dissolved in the prepared simvastatin nano suspension. Eudragit were added dropwise to the beaker containing HPMC and Simvastatin nano suspension. After that the polymeric dispersion was stirred continuously with the help of a magnetic The mixture was stirred until a clear solution was obtained. Dibutyl phthalate, serving as a plasticizer, and dimethyl sulfoxide, acting as a penetration enhancer, were then added to the polymer solution and stirred for an additional 30 minutes. The prepared homogeneous drug–polymer solution was poured into a petri dish, covered with aluminum foil, and allowed to evaporate at room temperature for 48 hours. The resulting dried patches were then stored in a desiccator.

## CHARACTERIZATION OF SIMVASTATIN NANO SUSPENSION INCORPORATED MATRIX FILM

The Simvastatin nano suspension was characterized using scanning electron microscopy (SEM) [13]. The particle size of the Simvastatin nano suspension was analyzed using a Zetasizer Nano-ZS90 (Malvern Instruments, UK) [14].

## EVALUATION OF TRANSDERMAL PATCH

### Physical appearance

Each transdermal patch was examined for color, surface smoothness, and uniformity of drug content [15].

### Thickness and weight variation

The thickness of the prepared films was measured at multiple points using a Digital Vernier Caliper (Mitutoyo, Japan), and the average value was recorded [16]. Weight variation tests were performed on three randomly selected patches (2.5 cm2) from each batch using an analytical balance (Shimadzu, Japan).

### Folding endurance

A section of the film (2.5 $cm^2$) was cut and repeatedly folded at the same location until tearing occurred. The folding endurance was recorded as the number of folds the film could withstand at the same point without breaking or cracking [17].

### Drug content

A transdermal patch of predetermined surface area of 2.5 $cm^2$, taken in a 100 mL volumetric flask containing methanol. The mixture was sonicated and then left for 24 h. The fluid was then filtered using a membrane that has a pore size of 0.45 µm. Lastly, the amount of medication in the solution was quantified with the help of a UV spectrophotometer by Shimadzu at 239 nm and absorbance was measured and data recorded. [18].

### Percentage moisture content

Each patch was weighed, stored in a desiccator with fused calcium chloride at room temperature, reweighed after 24 hours, and the average moisture loss calculated [19].

$$\text{Percentage moisture content (\%)} = \frac{[Initial\ weight - Final\ weight]}{Final\ weight} \times 100$$

**Percentage moisture uptake**

Each patch was weighed, placed in a desiccator with saturated potassium chloride, reweighed after 24 hours, and the average percentage moisture uptake calculated [20].

$$\text{Percentage moisture content (\%)} = \frac{[Final\ weight - Initial\ weight]}{Initial\ weight} \times 100$$

## STABILITY STUDY

Stability experiments were conducted for 45 days at 40±0.5°C and 75±5%RH, following ICH recommendations. The samples were obtained at the 15th, 30th, and 45th day intervals and were examined [21].

## RESULTS AND DISCUSSION

**Table 3: Formulation particle size and zeta potiential determination of Simvastatin nano suspension**

| Run | Homogenization cycles | Homogenization time | Sonication time | Particle size | Polydispersity index PDI | Zeta potential |
|---|---|---|---|---|---|---|
| | Minute | minute | minute | nm | | mV |
| **1** | 9000 | 30 | 15 | 604.6 | 0.623 | -36.7 |
| **2** | 10000 | 20 | 15 | 360 | 0.464 | -61.7 |
| **3** | 8000 | 20 | 15 | 964.7 | 0.671 | -62.6 |
| **4** | 9000 | 20 | 20 | 142.2 | 0.248 | -47.4 |
| **5** | 10000 | 30 | 20 | 130.8 | 0.308 | -52.0 |

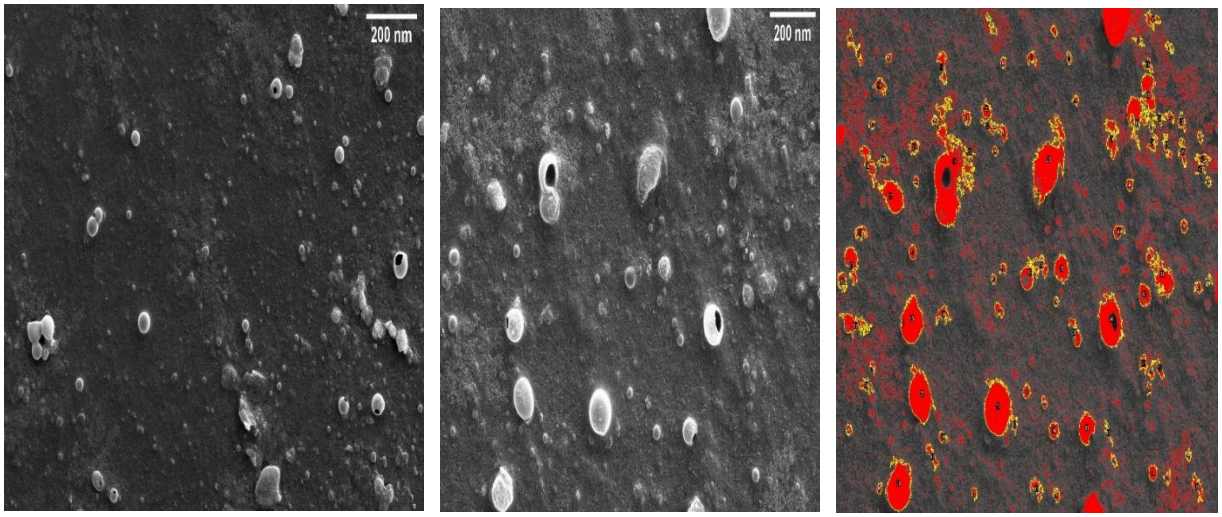


**Fig. 1: SEM images of Simvastatin nano suspension**

**Table 4: Evaluation of Simvastatin nano suspension incorporated transdermal patches**

| S,No | Properties | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | **Thickness (µm)** | 302.58 | 304.53 | 306.15 | 301.86 | 250.77 | 241.33 | 241.82 | 308.06 | 230.4 | 307.95 |
| **2** | **Weight variation (mg)** | 146.0 | 135.8 | 86.7 | 166.9 | 106.5 | 124.00 | 142.4 | 126.9 | 110.3 | 135.8 |
| **3** | **Folding endurance** | 296.6 | 285.3 | 265.8 | 296.5 | 276.4 | 295 | 290.8 | 292 | 272.8 | 309.8 |
| **4** | **Drug content** | 94.66 | 90.09 | 95.64 | 98.92 | 92.93 | 95.62 | 97.16 | 93.14 | 92.9 | 95.68 |
| **5** | **% moisture content** | 6.35 | 5.92 | 6.62 | 5.88 | 3.56 | 3.71 | 3.63 | 6.85 | 6.20 | 6.89 |
| **6** | **% moisture upatke** | 7.40 | 7.02 | 8.22 | 7.08 | 5.56 | 5.81 | 5.72 | 8.07 | 7.90 | 7.66 |

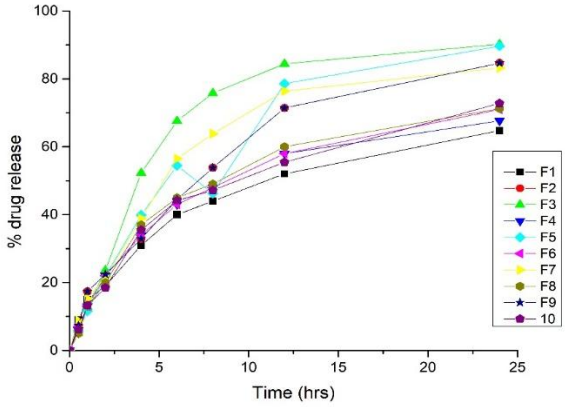


**Fig. 2: Cumulative parentage drug release of F1 to F10**

## KINETIC MODELLING OF DRUG RELEASE

Drug release patterns were analyzed using DDSolver software, fitting the release profiles to zero-order, first-order, and Higuchi kinetic models. Rate constants for different kinetic models of the drug are given in Tables 5. The results of different kinetics equations determined the drug release mechanism through the analysis of data by the correlation coefficient.The results of kinetic equations revealed that no release of Simvastatin from the formulation followed the release mechanism of zero order. All the prepared formulations presented the highest linearity toward Higuchi kinetics model except the formulation F3, F7 and F9. Millan B agrawal (2020) evaluated the release mechanism of nitrendipine from the polymeric combination of Eudragit and PVP patches. The prepared patches of nitrendipinefollowed the Higuchi model [22]. Higuchi described the drug released per unit area of patch and proportional to the time square root. It also described the hydrophilic drug release from the hydrophilic matrix by the help of Fick's law of diffusion [23]..

**Table 5: Release patterns of drug through different kinetic models**

| S,No | Formulation | Zero-order | First order | Higuchi |
|---|---|---|---|---|
| **1** | **F1** | 0.5363 | 0.8646 | 0.9785 |
| **2** | **F2** | 0.6900 | 0.9805 | 0.9774 |
| **3** | **F3** | 0.4663 | 0.9866 | 0.8968 |
| **4** | **F4** | 0.5350 | 0.8946 | 0.9622 |
| **5** | **F5** | 0.6436 | 0.9958 | 0.9498 |
| **6** | **F6** | 0.5836 | 0.9196 | 0.9760 |
| **7** | **F7** | 0.5417 | 0.9769 | 0.9393 |
| **8** | **F8** | 0.5665 | 0.9200 | 0.9622 |
| **9** | **F9** | 0.5161 | 0.9701 | 0.9316 |
| **10** | **F10** | 0.6257 | 0.9285 | 0.9753 |

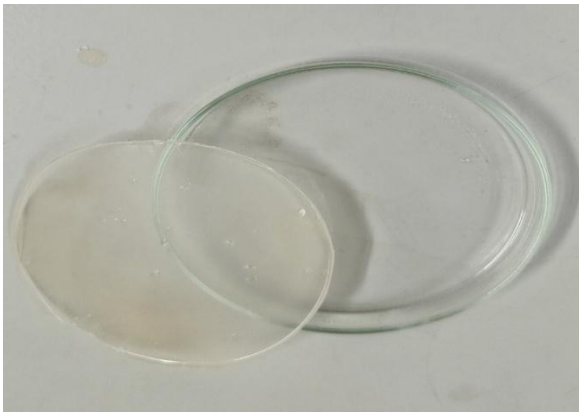

**Fig. 3: Transdermal film (F3 formulation)**

*S. Haritha V.Anod et al.* discovered a unique method, such as spherical agglomeration, resulted in an 80% drug release rate [24]. *A. M. Pethe et al.* reported that a simvastatin mucoadhesive buccal tablet released 65.96% of the medication [25]. In this study, the transdermal films achieved over 90% drug release, indicating that simvastatin delivery via this route offers higher release efficiency compared to other methods. Among the formulations, F3 demonstrated optimal physicochemical properties, including flexibility and maximum drug release, making it a promising candidate for dose reduction and enhanced patient compliance. As reported by *Idongesit Friday Etuk et al.,* polyethylene glycol is considered the most suitable plasticizer compared to alternatives like glycerin, as it offers superior physicochemical characteristics—such as optimal thickness, moisture uptake, and moisture absorption—along with an enhanced drug release profile [26]. *Wahyudin bin jamaludin et al.* found that transdermal films containing Dibutyl phthalate had maximum elasticity and were not brittle [27]. According to *Vijendra Pal Singh Rathore et al.,* formulation using Hydroxy propyl methylcellulose provided good folding endurance [28]. According to *Shubham Shivhare et al.,* increasing the amount of hydroxypropyl methylcellulose in the formulation enhanced both moisture uptake and moisture content [29]. The particle size was found, and it ranges between 964.7 nm and 130.8 nm. A formulation with lower size of 130.8 nm was selected for further studies, and its surface charge of zeta potential was negative give in table 3. The SEM image shows that nanoparticles were within the nano range shows in Fig 2.

The physicochemical characteristics of the films are presented in Table 4. The films weight were ranges from 86.7 to 147 mg due to variation of polymer concentration in each formulation. Thickness varied from 230.4 to 307.95 μm. Percentage drug content ranged from 90.09% to 97.16% in all the formulation. Percentage moisture content ranged from 3.71 to 6.89%. Moisture uptake ranged from 5.56 to 8.22%. Folding endurance tests yielded satisfactory results. The F3 formulation demonstrated the highest medication release. It was discovered that as the concentrations of HPMC and Eudragit RL100 increased, the drug release reduced. As a result, the formulation's good physiochemical properties were due to the addition of Dibutyl Phthalate and Dimethyl Sulfoxide.

## CONCLUSION

The transdermal films were successfully developed, with all formulations demonstrating desirable physicochemical properties. Findings revealed that both the type and concentration of the polymer had a significant impact on drug release, while higher concentrations of the penetration enhancer effectively increased drug permeation. Stability assessments indicated that the drug maintained its stability in the optimized transdermal film formulation. Collectively, these results indicate that the formulated films offer potential for simvastatin delivery with enhanced permeability.

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