FORMULATION, OPTIMIZATION AND EVALUATION OF MATRIX TYPE OF TRANSDERMAL SYSTEM OF SIMVASTATIN USING PERMEATION ENHANCERS

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ABSTRACT

The purpose of this research work was to develop matrix-type transdermal therapeutic system containing Simvastatin with different ratios of hydrophilic and hydrophobic polymeric combinations by the solvent evaporation technique. The physicochemical compatibility of the drug and the polymers were studied by infrared spectroscopy. Transdermal patches were prepared with different ratios of combination of polymers like HPMC + Ethyl cellulose and HPMC + Eudragit RL 100. The prepared patches were evaluated for different physicochemical evaluations like thickness, weight variation, folding endurance, tensile strength, percent flatness, swelling index, surface pH, water vapour transmission etc. in-vitro permeation and ex-vivo studies have done using Franz diffusion cell with dialysis membrane and goat skin respectively. The optimized batches were evaluated for permeation study by using permeation enhancers like 5% DMSO, 5% Oleic acid, 5% Eugenol and 5% Menthol. On the basis of in-vitro drug release and ex-vivo skin permeation study formulation F12D4 with menthol as permeation enhancer was found to be better than other formulation and it was selected as optimized formulation.

Keywords: Simvastatin, Transdermal, Ethyl cellulose (EC), HPMC, Eudragit RL100.

INTRODUCTION

Transdermal drug delivery is defined as self contained discrete dosage forms which, when applied to the intact skin, deliver the drug through the skin at controlled rate to the systemic circulation. Transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems. Transdermal delivery constitutes one of the most important routes for new drug delivery system. Transdermal delivery that traditionally uses a patch containing drug substance pressed on to the skin, is a non-invasive, convenient and painless and this approach to drug delivery offers many advantages over traditional methods. As a substitute for the oral route, transdermal drug delivery enables the avoidance of gastrointestinal absorption, with its associated pitfalls of enzymatic and pH associated deactivation. This method also allows for reduced pharmacological dosing due to the shortened metabolism pathway of the transdermal route versus the gastrointestinal pathway. The patch also permits constant dosing rather than the peaks and valleys in medication due to the shortened metabolization pathway of the transdermal delivery system. Multi-day therapy with a single application, rapid notification of medication in the event of emergency, as well as the capacity to terminate drug effects rapidly via patch removal.

Simvastatin is a lipid lowering-agent and widely used to treat hypercholesterolemia and it is a potent inhibitor of HMG-CoA reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol. Simvastatin is commercially available as tablets of 5mg, 10mg, 20mg, 40mg and 80mg strengths as immediate release dosage form. After oral administration bioavailability is only 5% due to extensive first pass metabolism in the liver. TDDS is considered to be the ideal method which can bypass the difficulties of first-pass metabolism, maintain the steady plasma level of drug for a prolonged period and deliver the drug at predetermined rate.

Simvastatin was chosen as the suitable candidate for this study since it possesses near ideal characteristics that a drug must have in formulating a transdermal drug delivery system: low molecular mass, high lipid solubility, effective in low plasma concentration as well as a high degree of first-pass metabolism. The aim of this study was to develop and evaluate transdermal patches of simvastatin so as to prevent its first-pass metabolism and achieve controlled release. These factors in addition to its low molecular weight (418.56 g/mol), low bioavailability (5%), low melting point (129°C), high lipid solubility and effective in low plasma concentration necessitates the formulation of sustained release transdermal drug delivery system for simvastatin.

In the present study various polymers like HPMC, Ethyl cellulose, and Eudragit RL100 were used due to its low toxicity, biocompatible, exhibits minimal cell adhesion, good chemical stability, film-forming ability. So the present aim of our work is to formulate and optimize a stable and controlled release transdermal formulation by using various polymers in order to avoid the first-pass effect, to obtain great therapeutic efficacy.

MATERIALS AND METHODS

Materials

Simvastatin was received as gift sample from Aurobindo pharma, Hyderabad. Ethyl cellulose, Hydroxy propyl methyl cellulose (HPMC) was procured from Himeda Laboratories Pvt Ltd, Mumbai. Eudragit RL 100 was purchased from Yarrow chem Products, Mumbai, and all other chemicals and reagents used in the study were of analytical grade.

Method

Drug-polymer compatibility study

The physicochemical interactions between Simvastatin and the polymers used in the formulation of transdermal patches HPMC, Eudragit RL 100 and EC were studied using Fourier transform infrared spectroscopy (FTIR). The infrared spectra were recorded in the FTIR (shimadzu) instrument in the wave length region between 4400 and 600 cm⁻¹ by KBr pellet method. The spectra obtained for drug, polymer and physical mixture of drug and polymer were recorded using the instrument in the same condition. The spectra were recorded for both pure drug and mixture and compared with the pure drug spectra. The difference between the pure drug and mixture spectra gives an indication of the interaction between the drug and the polymer.

Formulation of drug free patches

Matrix type transdermal patches of Simvastatin were prepared using different proportion of polymers like HPMC, Ethyl cellulose and Eudragit RL 100 by solvent evaporation technique. Polymers of different combination were accurately weighed and dissolved in methanol as a solvent. Propylene glycol 30% of polymer composition was used as plasticizer. The homogeneous dispersion by slow stirring with a magnetic stirrer. The uniform dispersion was casted on the PVA backing membrane casted earlier and dried at 40°C for 6h. After drying patches were removed, wapped with Aluminium foil and kept in desiccators until they were used for further study.
Formulation of drug incorporated transdermal patches

Matrix type transdermal patches of Simvastatin were prepared using different proportion of polymers like HPMC, Ethyl cellulose and Eudragit RL 100 by solvent evaporation technique. Polymers of different combination were accurately weighed and dissolved in methanol as a solvent. Propylene glycol 30% of polymer composition was used as plasticizer. The drug was added to the polymer solution and permeation enhancers also added. The uniform dispersion was casted on PVA backing membrane earlier and dried at 40°C for 6 h. After drying patches were removed and stored in desiccator for further study.

Evaluation of Transdermal Patches

**Thickness of the film**

The thickness of the patches was measured at five different points using screw guage. The average and standard deviation of five readings were calculated for each batch.

**Weight variation**

Weight variation was studied by taking individual weight of ten randomly selected patches for each formulation prepared in different batches. The weights were taken in electronic digital balance.

**Folding endurance test**

Folding endurance test was carried out by folding the patch at the same point a number of times till it broke. The test was carried out to check the efficiency of the plasticizer and the strength of the film prepared using varying ratios of the polymers. The test was carried out in triplicate.

**Percentage Moisture Loss**

Accurately weighed films of each formulation were kept in a desiccator and exposed to an atmosphere of 98% relative humidity (containing anhydrous calcium chloride) at room temperature and weighed after 3 days. The test was carried out in triplicate. The percentage of moisture loss was calculated as the difference between initial and final weight with respect to initial weight.

\[
\text{Percentage moisture loss} = \left(\frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}}\right) \times 100
\]

**Percentage moisture absorption**

Accurately weighed films of each formulation were kept in a desiccator which is maintained at 79.5% relative humidity (saturated solution of aluminium chloride) at room temperature and weighed after 3 days. The test was carried out in triplicate. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.

\[
\text{Percentage moisture absorption} = \left(\frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}}\right) \times 100
\]

**Tensile strength**

The tensile strength was determined by using a modified pulley system. Weight was gradually increased so as to increase the pulling force till the patch broke. The force required to break the film was considered as a tensile strength and it was calculated as N/m2.

**Flatness**

Three longitudinal strips were cut out from each film: one from the center, one from the left side, and one from the right side. The length of each strip was measured and the variation in length because of non uniformity in flatness was measured by determining percent contraction, with 0% contraction equivalent to 100% flatness.

\[
\text{Percent flatness (\%)} = \left(\frac{L1 + L2}{L1} \times 100\right)
\]

Where,

- L1 - initial length of strip
- L2 - final length of strip

**Swelling index**

The patches of 3.14 cm² was weighed and put in a Petridish containing 10 ml of double distilled water and were allowed to imbibe. Increase in weight of the patch was determined at preset time intervals, until a constant weight was observed. The degree of swelling (% S) was calculated using the formula

\[
S (\%) = \left(\frac{Wt - Wo}{Wo}\right) \times 100
\]

Where S is percent swelling, Wt is the weight of patch at time t and Wo is the weight of patch at time zero.

**Surface pH**

For the determination of surface pH the patches were left to swell for 2 h on the surface of agar plate, prepared by dissolving 2% (w/v) agar in warmed phosphate buffer (pH 6.8) under stirring and then pouring the solution into the petri dish till gelling at room temperature. The surface pH was measured by means of pH paper placed on the surface of swollen patches. The mean of three readings was recorded.

**Water vapour transmission rate**

Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in an oven. About 1gm anhydrous calcium chloride was placed in the cells and the respective polymer films were fixed over the brim. The cells were accurately weighed and kept in a closed desiccators containing saturated solution of potassium chloride to maintain a humidity of 84%. The cells were taken out and weighed after 6, 12, 24, 36, 48 and 72 hrs of storage. The amount of water vapour transmitted was found using the formula.

\[
\text{Water vapour transmission rate} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100
\]

**Drug content uniformity of films**

The patches (1cm²) were cut and added to a beaker containing 100 ml of phosphate buffered of pH 6.8. The medium was stirred with magnetic bead. The contents were filtered using whatman filter paper and the filtrate was examined for the drug content against the reference solution consisting of placebo films (contains no drug) at 238 nm spectrophotometrically. The experiment was repeated to validate the result.

**In-vitro Permeation Studies using dialysis membrane**

In vitro permeation studies were performed through dialysis membrane-50 (Hi Media) by using Franz diffusion cell apparatus with a receptor compartment capacity of 25 ml and cross sectional area of 3.14cm². The formulated patches were placed over the membrane facing the matrix side in contact with the membrane. The patches were withdrawn at different time intervals and analyzed for drug. One ml of receptor solution was withdrawn and an equal volume of fresh buffer was replaced. The samples are analyzed for drug content in spectrophotometer (Shimzhu UV-Vis, Model -1800) at 238 nm. The cumulative amounts of drug permeated per square centimeter of patches were plotted against time in hr.

**Ex-vivo permeation studies using goat skin**

**Preparation of goat skin**

Fresh Abdominal skin of goat were collected from slaughterhouse and used in the permeation experiments. Abdominal skin hairs were removed and the skin was hydrated in normal saline solution. The adipose tissue layer of the skin was removed by rubbing with a cotton swab. Skin was kept in isopropyl alcohol solution and stored at 0-40°C.
The transdermal permeation was performed in Franz Diffusion cell. The cells were filled with freshly prepared phosphate buffer pH 6.8. While placing the patch, the donor compartment contains patch on stratum corneum side of skin and dermis side was facing receptor compartment. Receptor compartment contains phosphate buffer pH 6.8, and samples were withdrawn at regular time intervals and replaced the same with receptor fluid. The samples were analyzed at 238 nm against blank by UV spectrophotometer

Scanning Electron Microscopy (SEM)

- The surface morphologies of the transdermal patch were investigated by using Scanning Electron Microscope, model JSM-6390, Prior to examination, samples were gold coated to make them electrically conductive.

- **Kinetic study**

  To know the mechanism of drug release from these formulations, the data were treated according to first-order (log percentage of drug to be released vs time), Higuchi’s (percentage of drug released vs square root of time), and zero-order (percentage of drug released vs time) patterns.

**RESULTS AND DISCUSSION**

**Drug polymer compatibility study**

Physicochemical compatibility of drug and polymer The FT-IR spectral analysis of Simvastatin alone showed that the principal peaks were observed at wave numbers 3350.95, 3010.88, 2970.38, 1724.36, and 1697.36 cm⁻¹. (Fig. 1) confirming the purity of the drug. In the FT-IR spectra of the physical mixture of simvastatin, HPMC, Eudragit RL100 and EC the major peaks of Simvastatin were observed at wave numbers 3350.95, 3010.88, 2970.38, and 1724.36 cm⁻¹. However, some additional peaks were observed with the physical mixture, possibly because of the presence of polymers.

**Evaluation of prepared transdermal patches**

The prepared transdermal patches were evaluated for their physicochemical characteristics such as weight variation, thickness, weight variation, % moisture loss, % moisture absorption, water vapour transmission rate, folding endurance, tensile strength, swelling index, surface pH, drug content, and *in vitro* drug release and *ex vivo* permeation.

**Thickness of the film**

Transdermal patches were transparent, smooth, uniform and flexible. The thickness of the weights ranged between 0.360 ± 0.020 mg and 0.416 ± 0.015 mg. Low standard deviation values in the film thickness measurements ensured uniformity of the patches prepared by solvent evaporation method.

**Weight variation**

The weights ranged between 0.021± 0.0005 mg and 0.027 ± 0.0020 mg, which indicates that different batches patch weights, were relatively similar.

**Folding endurance**

The folding endurance measures the ability of patch to withstand the rupture, folding endurance was in the range between 150 to 204, results indicated that patches had optimum strength ensuring their integrity and applicability. The formulations F4 and F12 showed the highest folding endurance. The folding endurance of Eudragit patches is higher than patches containing Ethyl cellulose.

**Percentage moisture Loss**

The % moisture loss was found to be between 2.0 ± 0.2516 to 5.1 ± 0.2080 as shown in Table 3 and loss was found to increase with increasing concentration of hydrophilic polymers. The small moisture loss in the formulations helps the film to remain stable, brittle and free from complete drying.

**Percentage moisture absorption**

Percentage moisture absorption was found to be 2.0 ± 0.152 to 6.8± 0.416. The result revealed that the moisture absorption was found to increase with increasing concentration of hydrophilic polymers. Low moisture absorption protects the material from microbial contamination and bulkiness of the patches.

**Tensile strength**

As the concentration of hydrophilic polymer HPMC was increased there is increase in tensile strength, patches varied from 2.2×10⁻¹ N/m² to 4.1× 10⁻¹ N/m². The patches prepared from HPMC:EC (F4) and HPMC:Eudragit RL 100 (F12) showed more tensile strength than other patches.

**Percent flatness**

The results of flatness study showed that none of the formulations had the difference in the strip lengths before and after longitudinal cut, indicating 100% flatness, and thus they could maintain a smooth surface when applied onto the skin.

**Swelling index**

- The study of the hydration of polymers used in sustained release application affects drug release from controlled release matrix. The consequence of water uptake could be the formation of empty spaces within the patch that could make its structure less resistant to mechanical stresses. The HPMC: ERL 100 patches showed more pronounced swelling as compared to HPMC: ECPatches. It varied between 10.9% to 36.45%. The swellability varied with nature and composition of patches. Hydrophilic polymer showed considerable swelling, as it increases the surface wettability and consequently water penetration within the matrix.

**Surface pH**

- Surface pH of all the films exhibited uniformity in their values and they were found to be 6, indicates that no irritation will occur on the skin after applications of the patches.

**Water vapour transmission**

The patch formulated with HPMC showed maximum vapour transmission rate, ranged from 1.5×10⁻²±0.2087 to 4.5×10⁻²±0.1527 mg cm⁻²h⁻¹, which can be attributed to the hydrophilic nature of polymer. The casting of HPMC with rate controlling polymer Eudragit RL100 decrease the values of water permeation rate.

**Drug content uniformity of films**

The drug content uniformity of the prepared formulation have shown that the process used to prepared the transdermal film in this study was capable of giving film with uniform drug content. The result of drug content indicates that drug is uniformly dispersed in formulation. Percentage drug loading has shown in Table 3.

**In-vitro Permeation Studies using dialysis membrane**

Considering all the factors like tensile strength, better physicochemical properties, maximum drug loading patch quality surface smoothness, formulations were selected for invitro release studies using dialysis membrane. The cumulative percentage of release after 24 hours as shown in figure.

- The Medicated films (HPMC:EC) showed drug release in the following order F4D4>F4D3>F4D2>F4D1 (HPMC+EudragitRL100) showed F12D4>F12D3>F12D2>F12DL. Hence from the above data the maximum release was found to be F4D4 and F12D4.

- From the above two formulations it was concluded that the release pattern was controlled by combination of hydrophilic and hydrophobic polymers. Eudragit RL100, ethyl cellulose was insoluble in diffusion medium. Partitioning between hydrophobic polymers and diffusion medium was very less indicating that the membrane has retarded the release of drug from the reservoir.

**Ex-vivo permeation studies using goat skin**

- A skin permeation enhancement study was carried out for the above formulations by incorporating chemical permeation enhancers DMSO, oleic acid, eugenol and menthol. It was found that incorporation of DMSO in the patch formulations slightly increased
the permeation of drug through the skin. In case of menthol as the permeation enhancer the maximum percentage cumulative drug permeated per cm² of the formulations through the skin at the end of 24 hrs were found for F4D4; 78.88% and F12D4; 80.45% (Table). DMSO and oleic acid markedly enhanced the permeation rate of F4D4 and F12D4 transdermal formulation showed the highest enhancing effect. The penetration enhancement in the increasing order of Menthol>Eugenol>OLEIC acid>DMSO. The mechanism of action of various chemical permeation enhancers may be attributed to their activity on lipophilic matrix and/or hydrophilic protein gel in stratum corneum, which act through interaction with intercellular lipids, leading to disruption of their organization and increasing their fluidity. Some of them may also interact with intercellular protein, keratin denaturation. Menthol and eugenol were coming under the category of terpenes. The mechanism by which terpene increase stratum corneum permeability by disrupting intercellular lipid bilayers (Barry 1989, Cornwell 1991). Terpenes, with propylene glycol (PG) or ethanol have been extensively investigated as skin permeation enhancers for many drugs.

### Scanning electron microscopy

SEM photographs of the matrix patch was taken, surface morphology and dug distribution pattern of the transdermal patch should be studied from SEM (Figure 7).

### Release kinetics

The data was subjected to 1st order equation and the regression value was found to be in range of \( R^2 = 0.917-0.9887 \) which confirms 1st order release pattern.

### Table 1: Formulation of transdermal patches using HPMC and EC

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Formulation code</th>
<th>Ratio of polymer HPMC : E</th>
<th>Solvent (Methanol) Ml</th>
<th>Plasticizer( % w/w) of total polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F1</td>
<td>2:2</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>F2</td>
<td>2:4</td>
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<td>30</td>
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<td>3</td>
<td>F3</td>
<td>2:6</td>
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<td>4</td>
<td>F4</td>
<td>2:8</td>
<td>5</td>
<td>30</td>
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<td>5</td>
<td>F5</td>
<td>6:2</td>
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<td>4:2</td>
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</tr>
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<td>8</td>
<td>F8</td>
<td>2:2</td>
<td>5</td>
<td>30</td>
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</table>

### Table 2: Formulation of transdermal patches using HPMC and Eudragit RL 100

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Formulation code</th>
<th>Ratio of polymer HPMC:Eudragit RL 100</th>
<th>Solvent (Methanol) nl</th>
<th>Plasticizer(%w/w) of total polymer</th>
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<tr>
<td>1</td>
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<td>2:2</td>
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<td>3</td>
<td>F3</td>
<td>2:6</td>
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<td>4</td>
<td>F4</td>
<td>2:8</td>
<td>5</td>
<td>30</td>
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<td>8</td>
<td>F8</td>
<td>2:2</td>
<td>5</td>
<td>30</td>
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</table>

### Table 3: Preparation of drug loaded patches

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Dose of simvastatin(mg)</th>
<th>Percentage of drug loading (%)</th>
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<tbody>
<tr>
<td>F4D1</td>
<td>5</td>
<td>34</td>
</tr>
<tr>
<td>F4D2</td>
<td>6</td>
<td>56</td>
</tr>
<tr>
<td>F4D3</td>
<td>9</td>
<td>54</td>
</tr>
<tr>
<td>F4D4</td>
<td>10</td>
<td>58</td>
</tr>
<tr>
<td>F12D1</td>
<td>5</td>
<td>38</td>
</tr>
<tr>
<td>F12D2</td>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>F12D3</td>
<td>9</td>
<td>38</td>
</tr>
<tr>
<td>F12D4</td>
<td>10</td>
<td>62</td>
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### Table 4: List of Permeation Enhancers

<table>
<thead>
<tr>
<th>Permeation Enhancer</th>
<th>Concentration(% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMSO</td>
<td>5</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>5</td>
</tr>
<tr>
<td>Eugenol</td>
<td>5</td>
</tr>
<tr>
<td>Menthol</td>
<td>5</td>
</tr>
</tbody>
</table>

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Fig. 1: FTIR Spectrum of Simvastatin
Fig. 2: FTIR spectrum of HPMC

Fig. 3: IR Spectrum of Ethyl cellulose

Fig. 4: IR Spectrum of Eudragit RL 100

Fig. 5: IR Spectrum of Simvastatin + HPMC + Ethyl cellulose

Fig. 6: IR Spectrum of Simvastatin + HPMC + Eudragit RL 100
Fig. 7: Scanning Electron Micrograph of Simvastatin Loaded Transdermal Patch.

Fig. 8: *In Vitro* release of simvastatin from transdermal patches of F4D1-F4D4

Fig. 9: *In Vitro* release of simvastatin from transdermal patches of F12D1-F12D4
Table 5: Thickness, Folding endurance, Weight variation, Percent Flatness, Tensile strength of blank patches

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Formulation code</th>
<th>Thickness (mm)</th>
<th>Weight variation (gm)</th>
<th>Percent Flatness (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F1</td>
<td>0.24±0.010</td>
<td>0.021±0.0005</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>F2</td>
<td>0.25±0.010</td>
<td>0.022±0.0010</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>F3</td>
<td>0.24±0.032</td>
<td>0.023±0.0015</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>F4</td>
<td>0.22±0.032</td>
<td>0.023±0.0020</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>F5</td>
<td>0.27±0.010</td>
<td>0.025±0.0011</td>
<td>100</td>
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<tr>
<td>6</td>
<td>F6</td>
<td>0.28±0.052</td>
<td>0.022±0.0015</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>F7</td>
<td>0.23±0.037</td>
<td>0.024±0.0057</td>
<td>100</td>
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<tr>
<td>8</td>
<td>F8</td>
<td>0.21±0.045</td>
<td>0.027±0.0020</td>
<td>100</td>
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<td>9</td>
<td>F9</td>
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<td>0.021±0.0020</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>F10</td>
<td>0.28±0.043</td>
<td>0.021±0.0020</td>
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<tr>
<td>11</td>
<td>F11</td>
<td>0.28±0.043</td>
<td>0.025±0.0005</td>
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<tr>
<td>12</td>
<td>F12</td>
<td>0.25±0.026</td>
<td>0.020±0.0026</td>
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<tr>
<td>13</td>
<td>F13</td>
<td>0.29±0.020</td>
<td>0.023±0.0020</td>
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<tr>
<td>14</td>
<td>F14</td>
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<td>0.026±0.0015</td>
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<td>F15</td>
<td>0.29±0.020</td>
<td>0.024±0.0015</td>
<td>100</td>
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<tr>
<td>16</td>
<td>F16</td>
<td>0.29±0.025</td>
<td>0.026±0.0015</td>
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</table>
CONCLUSION

The kinetic parameters among the formulations showed that all the formulations provided 1st order kinetics. Based on the observations, it is concluded that HPMC: Eudragit RL100 showed better release over other polymer ratio for the development of TDDS for simvastatin and the formulation F12D4 with menthol as permeation enhancer may be used for further studies in transdermal formulations provided 1st order kinetics. Based on the observations, it is concluded that HPMC: Eudragit RL100 showed better release over other polymer ratio for the development of TDDS for simvastatin and the formulation F12D4 with menthol as permeation enhancer may be used for further pharmacokinetic pharmacodynamic studies in suitable animal models.

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