Formulation and in Vitro Evaluation of Controlled Release Transdermal Drug Delivery System of Simvastatin A Model Hypocholesterolemia Drug

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ABSTRACT

The intention of this research work was to develop a matrix-type transdermal drug delivery system (TDDS) containing simvastatin an antilipemic drug with different ratios of hydrophilic HPMC K100M and hydrophobic Eudragit RL100 & Eudragit RS100 polymers with surfactant Tween 80 and plasticizer glycerin by the solvent evaporation technique. The prepared films were evaluated for physicochemical properties. Matrix films were evaluated for their physicochemical characterization followed by in-vitro evaluation. The drug released rate was found to be increased when the concentration of the polymer decreases. The release rates by using three polymers are shown that the HPMC K100M showed faster release than Eudragit RL100 and Eudragit RS100 because due to hydrophilicity. Compared between Eudragit RL100 and Eudragit RS100, the release rate was slightly faster found in Eudragit RL100. The evaluation studies were carried out known as percentage moisture content, percentage moisture uptake, folding endurance, thickness, weight variation, physical appearance, UV-Visible spectrophotometer, FTIR study and quantitative estimation of the drug. It was shown by all the observations that the antilipemic drug simvastatin could serve as an appropriate candidate for TDDS that can improve the bioavailability.

Keywords: Simvastatin, Transdermal, HPMC K100M, Eudragit RL100, Eudragit RS100.

INTRODUCTION

TDDS has been in survival for a long time. In the past, the most usually applied systems were topically applied creams and ointments for dermatological disorders. The occurrence of systemic side effects with some of these formulations is investigative of absorption through the skin. For systemic treatment of the skin, a number of drugs have been applied. In reality, the word TDDS comprises all formulations having topically administered drug intended for the transport of active constituents into the systemic circulation. Transdermal therapeutic systems have been intended to provide controlled and continuous delivery of drugs via through the skin to the systemic circulation. The drug simvastatin is poor aqueous solubility; it becomes uncomfortable to grow in the market even though expressing the potential pharmacodynamic property. It is really useful to find suitable formulation approaches to improve aqueous solubility and thus bioavailability of poorly soluble drugs1-2. Simvastatin is usually used to treat hypercholesterolemia and a lipid lowering-agent and also a potent HMG-CoA reductase inhibitor. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, simvastatin inhibits this enzyme and decreases the cholesterol synthesis and decreases the blood cholesterol level, which would be an active step to treat hypercholesterolemia and mixed dyslipidemia patients and in the treatment of homozygous familial hypercholesterolemiaa3-5. The Simvastatin tablets are commercially available having different strengths 5 mg, 10 mg, 20 mg, 40 mg, and 80 mg as immediate release dosage form. Due to extensive first-pass metabolism in the liver, the simvastatin bioavailability is only 5% after oral administration. The Ideal method of drug delivery is considered TDDS, which can bypass the first-pass metabolism and continue the stable drug level in plasma for an extended period and deliver drug at a predetermined rate6. In this study the suitable candidate was chosen is simvastatin because it possesses adjacent ideal characteristics that a drug must have formulated a TDDS due to the high lipid solubility, low molecular mass, effective in low plasma concentration as well as a high degree of first-pass metabolism. The purpose of this study was to improve and evaluate transdermal patches of simvastatin in order to prevent its first-pass metabolism and attain controlled release7.

MATERIAL AND METHOD

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Table 1: Composition of all formulations F1 to F9.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
<th>Category</th>
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<tr>
<td>Simvastatin</td>
<td>175 mg</td>
<td>175 mg</td>
<td>175 mg</td>
<td>175 mg</td>
<td>175 mg</td>
<td>175 mg</td>
<td>175 mg</td>
<td>175 mg</td>
<td>175 mg</td>
<td>Hypo lipidemic</td>
</tr>
<tr>
<td>HPMC</td>
<td>1 g</td>
<td>750 mg</td>
<td>500 mg</td>
<td>1 g</td>
<td>750 mg</td>
<td>500 mg</td>
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<td>mg</td>
<td>mg</td>
<td>mg</td>
<td>mg</td>
<td>mg</td>
<td>mg</td>
<td>mg</td>
<td>mg</td>
<td>mg</td>
<td>Plasticiser</td>
</tr>
<tr>
<td>Eudragit RS100</td>
<td>1 g</td>
<td>1 g</td>
<td>750 mg</td>
<td>1 g</td>
<td>750 mg</td>
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<td>Solvent</td>
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<td>Methanol</td>
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<td>Water</td>
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<td>1 ml</td>
<td>1 ml</td>
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<td>1 ml</td>
<td>1 ml</td>
<td>Plasticizer</td>
</tr>
<tr>
<td>Tween 80</td>
<td>0.4 ml</td>
<td>0.4 ml</td>
<td>0.4 ml</td>
<td>0.4 ml</td>
<td>0.4 ml</td>
<td>0.4 ml</td>
<td>0.4 ml</td>
<td>0.4 ml</td>
<td>0.4 ml</td>
<td>Surfactant</td>
</tr>
<tr>
<td>Glycerin</td>
<td>0.6 ml</td>
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<td>0.6 ml</td>
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</tr>
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<td>Dissolution time</td>
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<td>12 hr</td>
<td>12 hr</td>
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<td></td>
</tr>
</tbody>
</table>

Materials
Simvastatin was collected as a gift sample from Unichem Pvt. Ltd, Mumba, India. Eudragit RS100, Eudragit RL100 was procured from Otto Chemicals Pvt. Ltd, Mumbai, India. HPMC K100M was purchased from Oxford Laboratories, Mumbai, India. In the study, used all other reagents and chemicals were contained analytical grade.15

Methods
Drug-polymer compatibility study
The physicochemical interactions between simvastatin and the polymers used in the formulation of transdermal patches HPMC K100M, Eudragit RL100, and Eudragit RS100 were studied using Fourier transform infrared spectroscopy (FTIR). The infrared spectra were recorded in the FTIR (Shimadzu) instrument in the wavelength region between 4400 cm⁻¹ and 500 cm⁻¹ by KBr pellet method. The spectra obtained from the drug and the physical mixture of the drug and polymer were compared.16

Preparation of pH 7.4 phosphate buffer
The disodium hydrogen phosphate 2.38 g and potassium dihydrogen phosphate 0.19 g were accurately weighed and into it, 250 ml of distilled water was added. Then sodium chloride 8.0 g was mixed in the above solution and with distilled water, the final volume was made up to 1000 ml. The pH adjusted to 7.4 if required.16,17

Preparation of standard plot in pH 7.4 phosphate buffer
In a 100 ml volumetric flask the pure drug simvastatin 100 mg was taken and added 30 ml of methanol and then remaining volume was adjusted by adding a pH 7.4 phosphate buffer. The resultant concentration was 1 mg/ml. From the above solution, 10 ml was withdrawn into another 100 ml volumetric flask and volume is made up to 100 ml adding pH 7.4 phosphate buffer and the resultant stock solution was 100 μg/ml. From the stock solution 0.5, 1, 1.5, 2, 2.5 and 3 ml volumes were transferred into the 10 ml volumetric flask and volume are made up to 10 ml to produce concentration 5, 10, 15, 20, 25 and 30 μg/ml. At, 239 nm the six sample absorbance is measured against a blank using UV-Visible spectrophotometer.16,17

Preparation of transdermal patches
The transdermal patches were prepared by a solvent evaporation method. Different polymers (HPMC K100M, Eudragit RL100, and Eudragit RS100) alone were accurately weighed and dissolved in 30 ml of solvent (9:1) Methanol: water. A known amount of glycerol was used as a plasticizer and Tween 80 used as a permeability enhancer and mixed thoroughly with the help of a magnetic stirrer. 175 mg of the drug was dissolved in the solution and mixed for 10 min. The resulted uniform solution was decanted into a petri dish having 6 cm diameter and for uniform evaporation, the funnel was kept in an inverted position on a petri dish and held for the evaporation in an oven. After, 24 hrs all the prepared dried films were brought out and packed in aluminum foils than stored in a desiccator.8,15,17

Evaluation of transdermal patches
Thickness
By applying a digital micrometer screw gauge the patch thickness was evaluated at three different places and the mean value was calculated.9,12

Folding endurance
By repeatedly folding the strip at the same place of each film (2x2 cm) till it broke, the folding endurance of patches were determined. The folding endurance value was defined as the number of times the film can be folded at the similar place without breaking.8,10,12

Weight variation
The weights of 10 randomly selected patches are required for each formulation and the weight variation was estimated. The weights were taken in electronic digital balance.8,10,12

Percent of moisture uptake
The films were weighed individually and kept in a desiccator containing activated silica at room temperature for 24 hrs. The films were weighed individually and repeated until they show a constant weight. The moisture percentage of the patches were determined according to the difference between final and initial weight with respect to final weight8,11,12

Percentage moisture loss

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The desiccators which contain anhydrous calcium chloride, the films were weighed accurately and held back. After 3 days, the films were taken out and weighed. The moisture loss was estimated by using below-given formula:

\[
\% \text{ moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100
\]

Drug content uniformity of films

The patches (2x2 cm) were cut and added to a beaker containing 100 ml of phosphate buffer saline of pH 7.4. The medium was stirred with the help of a magnetic bead. By using Whatman No. 1 filter paper the contents were filtered, and the filtrated drug content was examined again against the reference solution containing placebo films (containing no drug) spectrophotometrically at 239 nm. The experiment was repeated to validate the result.

In-vitro drug release studies

From the fabricated patch, a (2x2 cm) film was removed and placed in the semi-permeable membrane and attached to the modified diffusion cell such that the cell’s drug releasing surface towards the receptor compartment which was filled with 100 ml phosphate buffer solution of pH 7.4 at 37±0.5°C. The elution medium was stirred magnetically. At a predetermined time intervals (1 hr) the aliquots (5 ml) samples were withdrawn and replaced with the similar volume of pH 7.4 phosphate buffer. The samples were analyzed for drug content using UV-Visible spectrophotometer at 239 nm.

Kinetics of drug release

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero-order (total percentage of drug release versus time), first-order (log total percentage of drug remaining vs. time), Higuchi (total percentage of drug release versus the square root of time), Hixon-Crowell (cube root of drug percentage remaining in matrix versus time) and Korsmeyer-Peppas (log total percentage of drug release versus log time) respectively.

RESULT AND DISCUSSION

FTIR spectra of simvastatin alone and its combination with excipients are shown in Figure 2 & 3. An FTIR spectrum of pure simvastatin shows prominent peaks at 1658.70 cm⁻¹, 1592.90 cm⁻¹, 1520.07 cm⁻¹, 1433.76 cm⁻¹, 1224.03 cm⁻¹, 1155.65 cm⁻¹, 844.59 cm⁻¹, and 696.07 cm⁻¹. These peaks can be regarded as characteristic peaks of simvastatin were not affected and prominently observed in the FTIR spectra of simvastatin along with excipients as shown in Figure 3, which indicated that there was no interaction between drug and excipients. Transdermal patches of simvastatin were prepared by using polymers, like HPMC K100M, and Eudragit RL100 and Eudragit RS100. The patches were transparent, smooth and elastic. The physicochemical characteristics of prepared patches are shown in Table 2. Thickness was found from 0.146
mm to 0.195 mm in range. The F1 formulation was more thickness due to its high swellability when compared to other polymers and when the concentration increases the thickness also increases. Uniformity of drug content was
Table 3: In-vitro drug release kinetic studies of different formulations.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Zero-order</th>
<th>First-order</th>
<th>Higuchi</th>
<th>Hixon Crowell</th>
<th>Release Exponent (α)</th>
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<tbody>
<tr>
<td>F1</td>
<td>0.965</td>
<td>0.918</td>
<td>0.982</td>
<td>0.971</td>
<td>1.049</td>
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<tr>
<td>F2</td>
<td>0.95</td>
<td>0.838</td>
<td>0.884</td>
<td>0.9</td>
<td>0.738</td>
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<tr>
<td>F3</td>
<td>0.969</td>
<td>0.771</td>
<td>0.995</td>
<td>0.931</td>
<td>1.058</td>
</tr>
<tr>
<td>F4</td>
<td>0.964</td>
<td>0.953</td>
<td>0.994</td>
<td>0.985</td>
<td>0.82</td>
</tr>
<tr>
<td>F5</td>
<td>0.976</td>
<td>0.858</td>
<td>0.922</td>
<td>0.924</td>
<td>0.868</td>
</tr>
<tr>
<td>F6</td>
<td>0.967</td>
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<td>0.899</td>
<td>0.841</td>
<td>0.847</td>
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<tr>
<td>F7</td>
<td>0.87</td>
<td>0.977</td>
<td>0.941</td>
<td>0.957</td>
<td>1.42</td>
</tr>
<tr>
<td>F8</td>
<td>0.987</td>
<td>0.847</td>
<td>0.975</td>
<td>0.925</td>
<td>1.004</td>
</tr>
<tr>
<td>F9</td>
<td>0.992</td>
<td>0.771</td>
<td>0.972</td>
<td>0.892</td>
<td>0.762</td>
</tr>
</tbody>
</table>

CONCLUSION

All nine formulations were evaluated for thickness, folding endurance, moisture uptake, physical appearance and results found for all is satisfactory. By the study of all parameters, it was concluded that the transdermal patch F7 is a better formulation among all the prepared formulations. Drug-polymer compatibility studies by FTIR gave confirmation about their purity and showed no interaction between the drug and polymers. Various formulations were developed by using hydrophilic polymer like HPMC K100M and hydrophobic polymers like Eudragit RS100 and Eudragit RL100 respectively by the solvent evaporation technique with the incorporation of penetration enhancer such as Tween 80 and glycerol as plasticizer.

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REFERENCES