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# Formulation and Evaluation of Simvastatin Transdermal Drug Delivery System

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## Abstract

Transdermal patches are a cutting-edge drug delivery technology that is essential in the management of many disorders. As first-pass metabolism is avoided, TDDS can effectively increase bioavailability and aid in the delivery of drug molecules into the systemic circulation at a planned and controlled rate. This study's goal was to create matrix-type simvastatin transdermal patches utilising the solvent evaporation method and various polymer ratios, including HPMC 15 cps, HPMC E5, and Eudragit S 100. Plasticizers like glycerine, propylene glycol, and PEG 200 are utilised, along with solvents like methanol and chloroform. According to FTIR studies, pure drugs and excipients are compatible with each other. The tested patches are assessed for thickness, weight variation, folding endurance, moisture content, drug content, surface pH, and in vitro diffusion studies. The results indicated that the formulation F5 showed better characteristic properties and in vitro drug diffusion.

**Keywords:** Transdermal drug delivery system, Simvastatin, HPMC 15cps, Eudragit S100, HPMC E5.



## 1. INTRODUCTION

Transdermal drug delivery system (TDDS), is a self-contained discrete dosage form which when applied in to the intact skin it delivers the drug molecules into the systemic circulation at a controlled and predetermined rate [1-3). TDDS aids in the avoidance of first pass metabolism and GI irritation of drugs, increasing bioavailability and decreasing the harmful side effects, resulting in effective drug delivery [4-6].

Mechanism of transdermal drug delivery system occurs through passive diffusion. There are three main pathways through which the drug permeation occurs they are, trans appendageal route, transcellular route and intercellular route. Drug absorption pathway may differ depending upon the physicochemical properties of the drug molecules [7, 8].

Simvastatin is an antihyperlipidemic drug that belongs to the HMG-CoA reductase inhibitor class. It aids in the treatment of atherosclerosis and heart attacks. Simvastatin works as a reversible competitive inhibitor of HMG-Co A, which binds to the HMG Co-A reductase [9-11].

Simvastatin is a lipophilic drug. Because of its significant first pass metabolism, simvastatin has a plasma half life of 2 hours and an oral bioavailability of 5% [12]. Simvastatin is an ideal candidate for transdermal patch formulation due to its physicochemical characteristics such as low melting point, high lipid solubility, low molecular weight, and biological characteristics such as highly potent, extensive first pass metabolism, and low bioavailability [13].

Simvastatin is developed as transdermal patches to overcome the extensive first pass Metabolism and to increase bioavailability. As a result, the drug is released into the systemic circulation in a controlled manner [14].

## 2. MATERIALS AND METHODS

Simvastatin was obtained as a gift sample from Covalent laboratories Pvt. Ltd, Hyd.HPMC 15 cps, HPMC E5 was obtained from AR chemicals, HYd.The remaining chemicals and reagents were of analytical quality.

**2.1 UV spectrophotometric method for Simvastatin in pH 7.4 phosphate buffer:**

Standard stock solution is prepared by taking 100mg of simvastatin and dissolve in few ml of methanol and finally make up the volume up to 100 ml with phosphate buffer to get the concentration of 1000ppm (Stock A).From this stock solution A, pipette out 10 ml and it was further diluted with phosphate buffer to obtain the solution of 100ppm (Stock B). From this stock solution B, pipette out 1ml and it was further diluted with phosphate buffer to obtain the solution of 10ppm.and scanned for $\lambda max$ from 400 to 200 nm on UV spectrophotometer.

**2.2 Calibration curve of Simvastatin in pH 7.4 phosphate buffer:**

From stock solution B, pipette out aliquots of 0.2,0.4,0.6,0.8,1.0. they are diluted with phosphate buffer in 10 ml volumetric flask to get the concentrations of 2,4,6,8 and 10. ppm respectively. Absorbance of each was taken at $\lambda max$ with phosphate buffer as blank and plotted against concentration and find out the value of regression coefficient.

**2.3 Drug-excipient compatibility studies by FT-IR:**

Drug excipient compatibility studies can be determined by FTIR. By analysing with pure drug and physical mixture of both drug and excipients.

**2.4 Method of preparation of Simvastatin transdermal patches:**

Matrix type transdermal patches containing simvastatin were prepared by solvent evaporation technique, using different ratios of HPMCE5, HPMC15cps and Eudragit S 100, were weighted in requisite ratios for patch preparation and they are allowed for swelling for about 6hrs in a solvent mixture and plasticizer PEG 200 or Propylene glycol was added. After that, the drug solution was mixed with the polymeric solution. Casted on to petri plate, and it is allowed for air drying overnight followed by vacuum drying for 8-10hrs.

**Table-1: Formulation table of Simvastatin transdermal patches**

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Drug (mg) | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| HPMC 15 cps (mg) | 26.3 | 26.3 | - | - | 13.15 | 13.15 | - | 13.15 | 6.57 | 6.57 | 13.15 | 13.15 |
| HPMC E 5 | - | - | 26.3 | - | 13.15 | - | 13.15 | 6.57 | 13.15 | 6.57 | 13.15 | - |
| Eudragit S 100 (mg) | - | - | - | 26.3 | - | 13.15 | 13.15 | 6.57 | 6.57 | 13.15 | - | 13.15 |
| Methanol (ml) | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Chloroform(ml) | | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Water (ml) | 0.5 | - | - | - | - | - | - | - | - | - | - | - |
| PEG 200 (ml) | 0.05 | - | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | - | 0.05 |
| Propylene glycol (ml) | - | 0.05 | - | - | - | - | - | - | - | - | 0.05 | - |
| Glycerin (ml) | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 |

**2.5 Evaluation tests [15-22]:**

**a) Weight variation:**

Weight variation was determined by cutting the transdermal patch into 2 cm square and the weight of 3 patches was determined and the average weight was calculated.

**b) Thickness:**

The thickness of 3 patches were determined by using Vernier calipers. Thickness was measured at three different points on the patch and the average readings were recorded.

**c) Folding endurance:**

A Patch of 2cm square was cut evenly and repeatedly folded at the same place till it brakes. The value of the folding endurance is determined by the number of times the film was folded at the same location without breaking.

**d) Surface pH:**

Films of 2 cm square are placed in 0.5ml of double distilled water in a glass tube for about 1 hour and pH of the film was calculated using pH meter.

**e) Drug content:**

Films of 2cm square are placed in a mixture of 20ml Methanol and 80ml pH 7.4 phosphate buffer in 100ml volumetric flask and stirred by using magnetic stirrer for 24 hours. Drug solution was scanned in UV spectroscopy and drug content was calculated.

**f) Percentage of moisture content:**

Films of 2 cm square are weighed individually and stored in a desiccator for about 24hrs at room temperature and moisture content was calculated using formula:

Moisture content = initial weight – final weight\ final weight×100

**g) In vitro drug diffusion studies:**

In vitro drug release studies is performed by using Franz diffusion cell. It consists of receptor compartment of 22.5ml capacity and it also contains donor compartment. The receptor compartment was filled with pH 7.4 phosphate buffer cellophane membrane was Placed between the donor and receptor compartment. The prepared transdermal patch was placed on cellophane membrane. The whole assembly was fixed on a magnetic stirrer and continuously stirred at 50rpm.The temperature was maintained at 32 ± 0.5

ºC. The samples were withdrawn at different time intervals and analyzed in UV spectroscopy. The receptor chamber was replenished with an equal amount of pH 7.4 phosphate buffer to Maintain sink conditions. A graph was plotted between cumulative percentage of drug permeation per square cm of patches against time.

## 3. RESULTS AND DISCUSSION

### 3.1 UV spectrum of Simvastatin in pH 7.4 phosphate buffer:

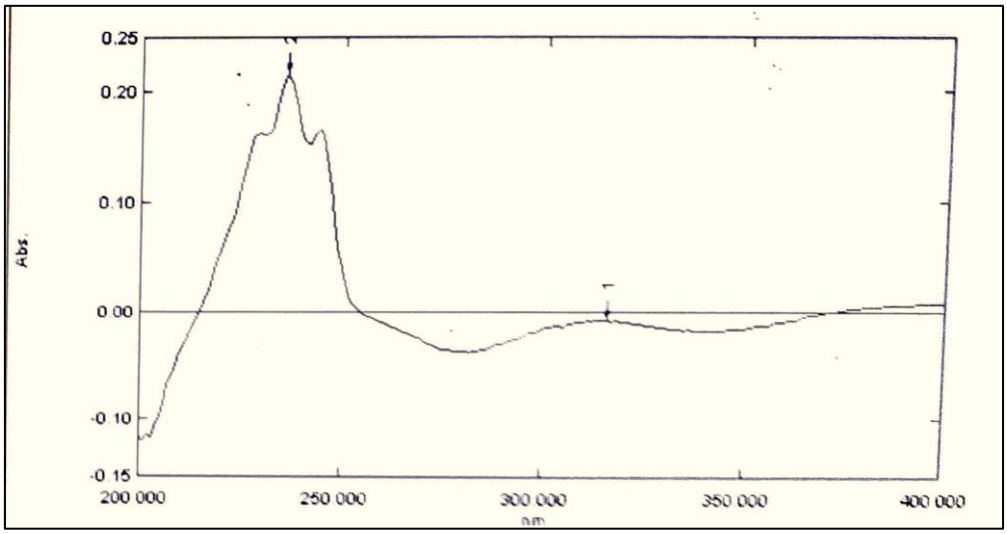


**Fig-1: UV spectrum of Simvastatin in pH 7.4 phosphate buffer**

Maximum absorption was found at 236 nm

### 3.2 Calibration curve of Simvastatin in pH 7.4 phosphate buffer:

**Table-2: Calibration curve of Simvastatin in pH 7.4 phosphate buffer**

| Concentration(ppm) | Absorbance |
|---|---|
| 2.00 | 0.124 |
| 4.00 | 0.172 |
| 6.00 | 0.225 |
| 8.00 | 0.271 |
| 10.00 | 0.318 |

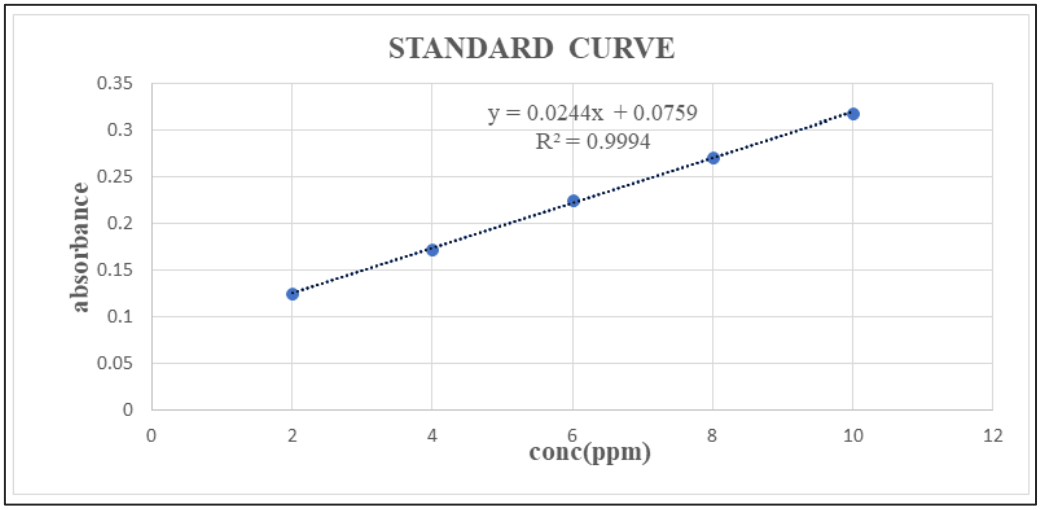


**Fig-2: Calibration curve of simvastatin in pH 7.4 phosphate buffer**

The graph was found to be linear and $R^2$ was found to be 0.9994

### 3.3 FTIR spectrum of Simvastatin:

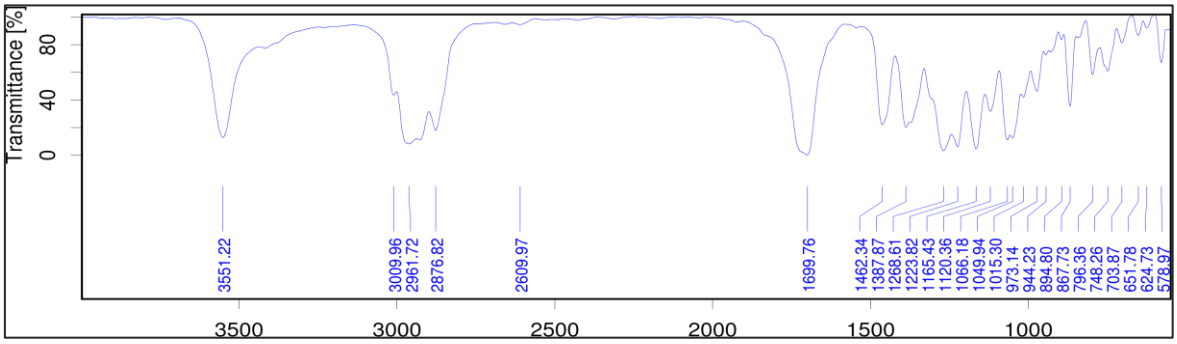


**Fig-3: FTIR spectrum of Simvastatin**

### 3.4 FTIR spectrum of Formulation F5:

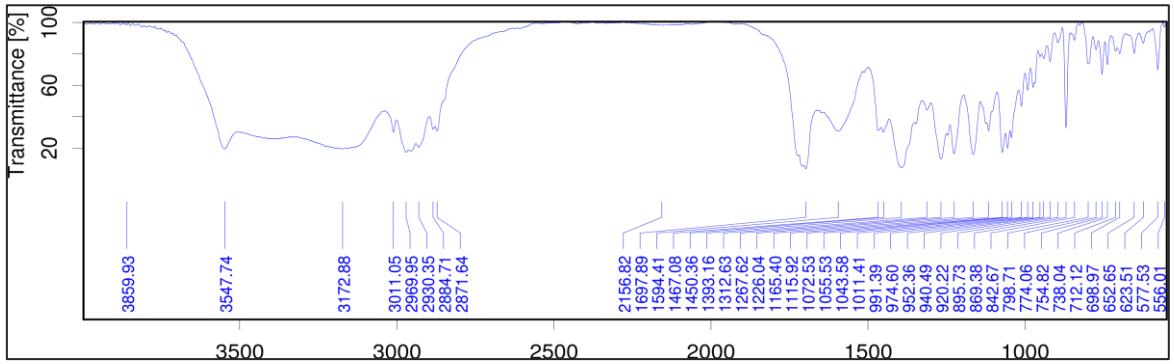


**Fig-4: FTIR spectrum of Formulation F5**

Both pure drug and excipients are compatible with each other.

### 3.5 Evaluation tests

**Table-3: Evaluation tests of Simvastatin transdermal patches**

| S. NO | %weight variation SD ± n=3 | Thickness (mm)SD ± n =3 | Folding endurance SD ± n=3 | Surface pH SD ± n=3 | Drug content SD ± n=3 | %moisture content SD ± n = 3 |
|---|---|---|---|---|---|---|
| **F1** | 6.95 ± 0.03 | 0.26 ± 0.30 | 277 ± 3 | 6.01 ± 0.05 | 97.49±0.03 | 1.98 ± 0.06 |
| **F2** | 5.52 ± 0.86 | 0.23 ± 0.11 | 326 ± 2 | 5.98 ± 0.02 | 90.12±0.01 | 2.21 ± 0.07 |
| **F3** | 3.74 ± 0.02 | 0.28 ± 0.12 | 294 ± 2 | 5.92 ± 0.07 | 88.23±0.02 | 1.30 ± 0.012 |
| **F4** | 4.63± 0.081 | 0.27 ± 0.09 | 280 ± 4 | 6.03 ± 0.01 | 75.54±0.08 | 2.36 ± 0.14 |
| **F5** | 0.09 ± 0.05 | 0.21 ± 0.3 | 350 ± 3 | 6.10 ± 0.12 | 99.23±0.02 | 1.36 ± 0.01 |
| **F6** | 2.08 ± 0.04 | 0.25 ± 0.80 | 290 ± 3 | 6.05 ± 0.10 | 82.56±0.09 | 1.52 ± 0.26 |
| **F7** | 2.6 ± 0.05 | 0.23 ± 0.41 | 310 ± 2 | 6.03 ± 0.15 | 91.12±0.08 | 1.42 ± 0.07 |
| **F8** | 11.6± 0.024 | 0.24 ± 0.26 | 300 ± 4 | 5.89 ± 0.03 | 89.54±0.05 | 1.98 ± 0.01 |
| **F9** | 1.32 ± 0.86 | 0.23 ± 0.08 | 280 ± 2 | 5.86 ± 0.01 | 86.67±0.06 | 2.21 ± 0.06 |
| **F10** | 2.48± 0.024 | 0.28 ± 0.09 | 289 ± 3 | 5.96 ± 0.05 | 72.34±0.09 | 2.45 ± 0.15 |
| **F11** | 6.35± 0.002 | 0.26 ± 0.07 | 290 ± 3 | 5.25 ± 0.08 | 82.79±0.03 | 1.49 ± 0.62 |
| **F12** | 0.09 ± 0.02 | 0.21 ± 0.3 | 3049 ± 3 | 6.9± 0.12 | 98.23±0.02 | 1.35 ± 0.01 |

Weight variation was measured for all the formulations and weight variation was found to be in the range of 0.09to 11.6± 0.05 values of weight variation are shown in the Table-3.

Thickness was measured for all the formulations and thickness was found to be in the range of 0.21to0.28 ± 0.3 values of thickness are shown in the table-3.

Folding endurance was measured for all the formulations and Folding endurance was found to be in the range of 277 to 350 ± 3 values of Folding endurance are shown in the Table-3.

Surface pH was measured for all the formulations and surface pH was found to be in the range of 5.86 to 6.10 ± 0.05. values of surface pH are shown in the Table-3.

Drug content was measured for all the formulations and drug content was found to be in the range of 72.34 to 99.23± 0.006. values of drug contents are shown in the Table-3.

%Moisture content was measured for all the formulations and % Moisture content was found to be in the range of 1.36 to 2.45± 0.07. values of % moisture content is shown in the Table-3.

### 3.6 In vitro drug diffusion studies:

**Table-4: In vitro drug diffusion studies of F1 to F6**

| TIME (hrs) | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| **0** | 0 | 0 | 0 | 0 | 0 | 0 |
| **0.25** | 3.21±0.63 | 5.42±0.53 | 3.32±0.62 | 3.25±0.74 | 2.25±0.53 | 3.21±0.63 |
| **0.5** | 10.26±1.54 | 10.51±0.92 | 9.31±0.91 | 9.45±0.83 | 3.89±0.64 | 10.23±0.54 |
| **1** | 23.41±3.72 | 22.12±1.81 | 13.25±1.83 | 21.25±2.54 | 7.03±1.53 | 25.23±1.74 |
| **2** | 40.23±5.56 | 42.43±3.73 | 48.12±2.71 | 40.03±3.63 | 14.65±2.73 | 36.43±1.65 |
| **4** | 73.65±5.73 | 63.61±4.62 | 58.15±2.52 | 56.26±2.52 | 26.72±3.54 | 47.62±2.75 |
| **6** | 91.45±6.52 | 76.35±6.53 | 67.21±3.63 | 67.52±6.63 | 38.67±3.64 | 58.47±2.83 |
| **8** | - | 89.84±5.32 | 83.23±3.71 | 79.89±4.73 | 49.31±4.42 | 69.97±5.54 |
| **12** | - | - | 92.14±4.82 | 89.98±4.84 | 54.72±3.64 | 80.37±6.64 |
| **16** | - | - | - | - | 75.58±6.81 | 91.62±4.74 |
| **24** | - | - | - | - | 98.14±5.51 | - |

**Table-5: In vitro drug diffusion studies of F7 to F12**

| TIME (hrs) | F7 | F8 | F9 | F10 | F11 | F12 |
|---|---|---|---|---|---|---|
| **0** | 0 | 0 | 0 | 0 | 0 | 0 |
| **0.25** | 4.23±0.43 | 5.27±0.54 | 4.35±1.45 | 4.41±0.73 | 3.42±2.83 | 3.47±1.73 |
| **0.5** | 13.56±1.65 | 13.41±1.64 | 12.25±1.64 | 16.24±1.54 | 13.35±3.54 | 15.65±2.54 |
| **1** | 26.12±1.74 | 25.22±1.73 | 20.57±2.75 | 23.03±2.64 | 24.51±2.64 | 25.54±2.64 |
| **2** | 48.42±2.64 | 45.51±2.83 | 50.26±0.83 | 58.24±3.75 | 48.82±3.73 | 43.54±3.73 |
| **4** | 76.02±3.53 | 57.43±1.93 | 65.36±1.92 | 70.76±4.63 | 56.22±4.53 | 59.78±4.67 |
| **6** | 90.23±4.73 | 67.27±2.53 | 78.54±2.54 | 81.64±5.73 | 67.54±5.63 | 69.23±4.75 |
| **8** | - | 78.56±3.63 | 90.58±4.76 | 92.34±4.83 | 76.54±3.56 | 81.24±5.83 |
| **12** | - | 92.14±5.74 | - | - | 83.12±5.74 | 87.45±4.73 |
| **16** | - | - | - | - | 91.14±3.84 | - |
| **24** | - | - | - | - | - | - |

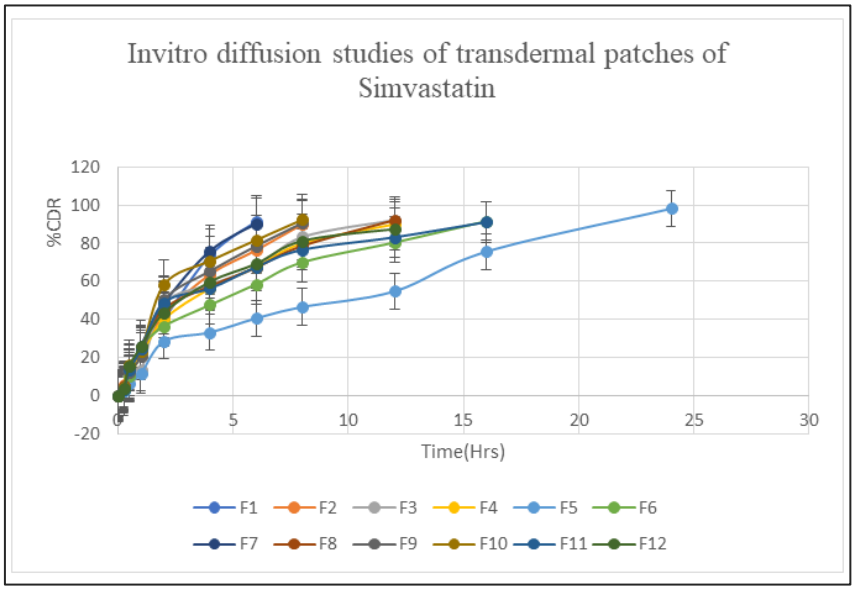


**Fig-5: In vitro drug diffusion studies of F1 to F12**

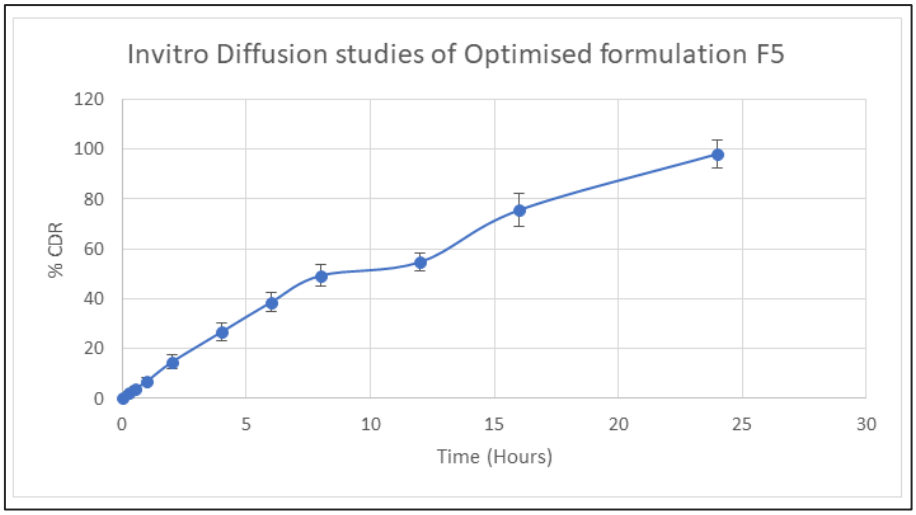


**Fig-6: In vitro diffusion of Simvastatin Optimized Formulation (F5)**

The data obtained from the in vitro drug diffusion studies is shown in the table-4 and 5. In vitro drug diffusion studies are performed for 24 hours. All the prepared patches have shown controlled release with in a range for 6 hrs to 16 hrs except F5 (24hrs).In vitro drug diffusion studies are carried out using pH 7.4 phosphate buffer At 236nm.Among them F5 shows highest drug release at the end of 24$^{th}$hour.so, F5 formulation chosen as the best formulation as it releases the drug at a slow rate for longer duration of time.

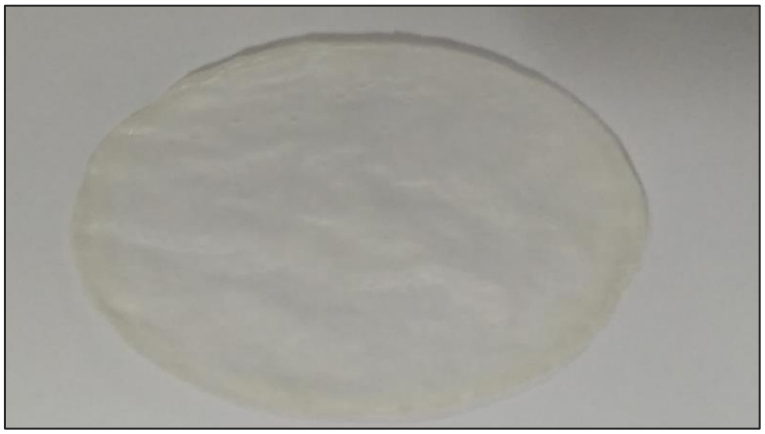

**Fig-7: Best formulation F5**

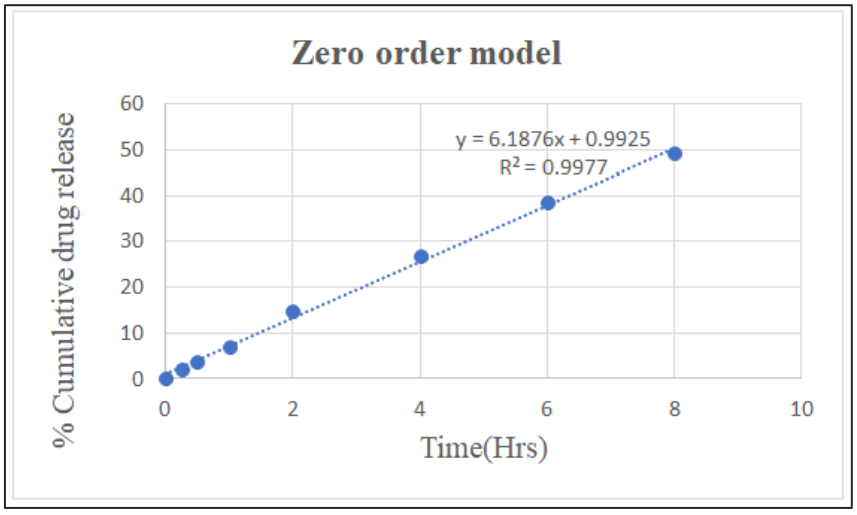


**Fig-8: Zero order release kinetics for best formulation (F5)**

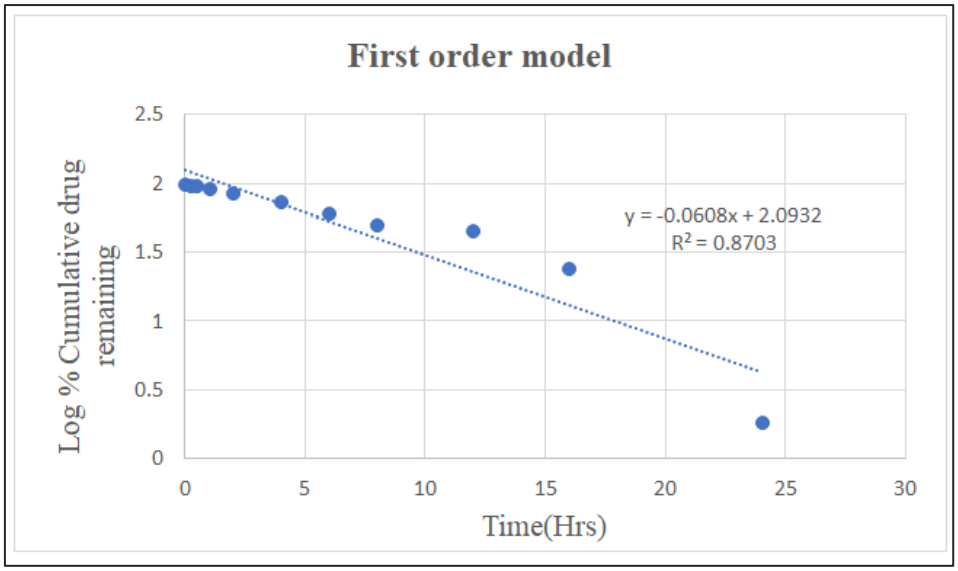


**Fig-9: First order release kinetics for best formulation (F5)**

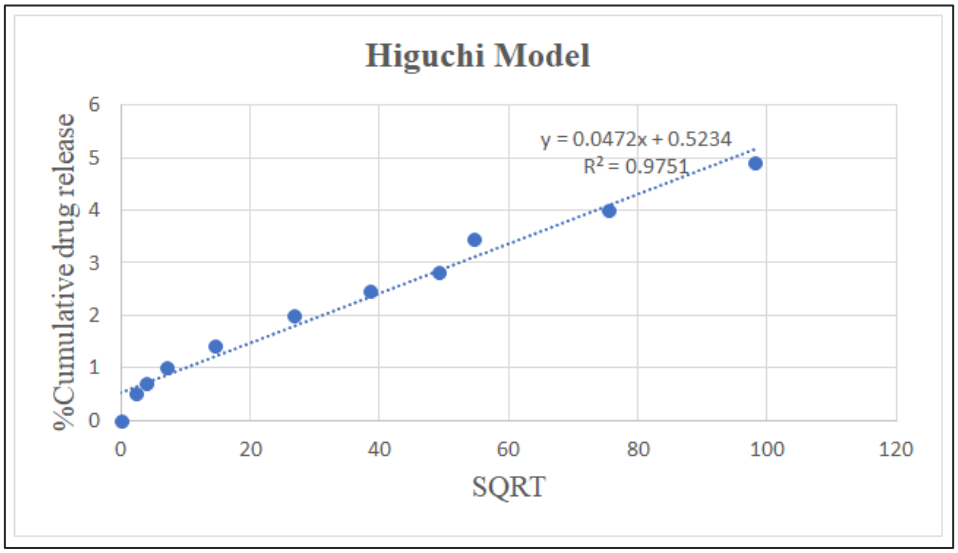


**Fig-10: Higuchi release kinetics for best formulation (F5)**

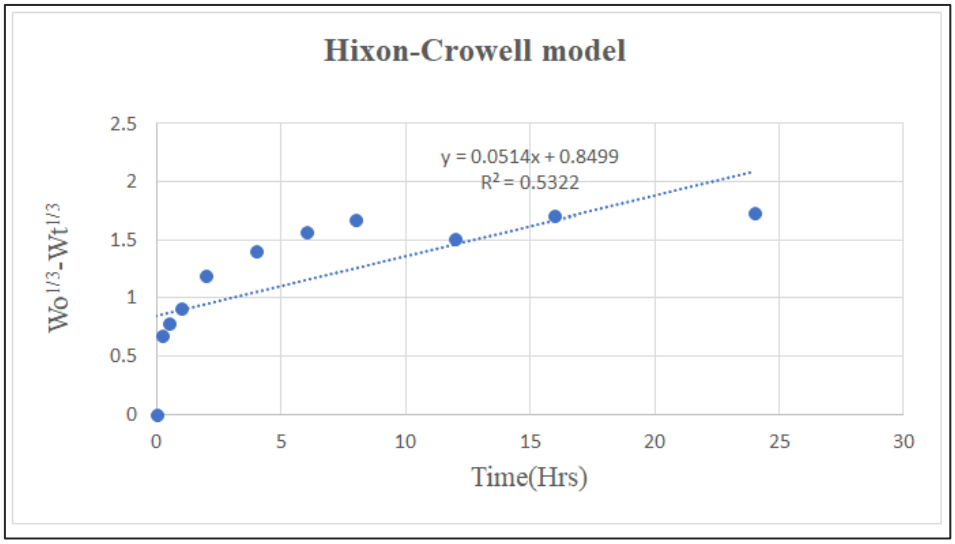


**Fig-11: Hixon-Crowell release kinetics for best formulation (F5)**

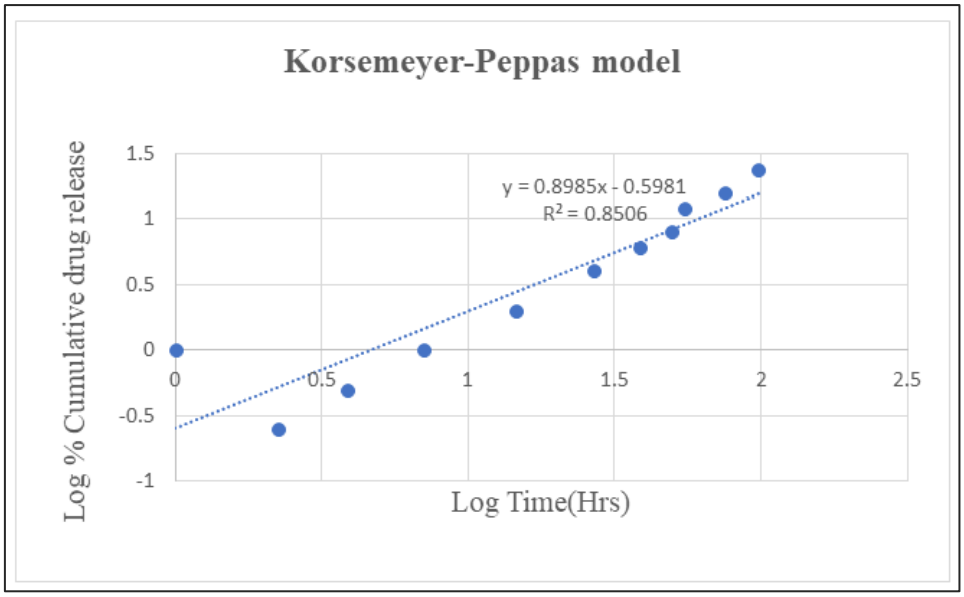


**Fig-12: Korsemeyer-Peppas release kinetics for best formulation (F5)**

## 4. CONCLUSION

Among all the formulations prepared F5 shows best results. All the physicochemical properties of F5 were found to be satisfactory. The patch exhibit - controlled release over 24 hours. The results of the study shows that Simvastatin can be delivered by Transdermal patches. The results of the current investigation suggest that the transdermal patch containing Simvastatin may have great promising for effective doses to systemic circulation.

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