Original Article

Preparation and Characterization of Transdermal Therapeutic System Containing Simvastatin: A Statistical Study

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ABSTRACT

Introduction: The purpose of the present study was to design, develop, and characterize the transdermal patches containing Simvastatin for the management of blood lipid levels. **Materials and Methods:** Transdermal patches of Simvastatin were prepared by the solvent casting method. The prepared patches were evaluated for physicochemical characteristics such as thickness, weight variation, folding endurance, percentage moisture uptake, percentage moisture content, percentage drug content, and *ex-vivo* permeation study. Eudragit polymer grades ERL100 and ERS100 were used in 6:4 and 8:2 ratio to prepare the formulations. Formulations were prepared using 2^3 factorial designs. Stability studies of the films were subjected to the environmental conditions at a temperature of 45°C, 75% relative humidity for 45 days. **Results:** The permeation parameters like flux, amount of drug permeated, and permeability coefficient were obtained. It was found that all these values were highest for formulation F8. **Conclusion:** Based on all parameters, formulation F8 was considered as the best formulation.

Key words: Transdermal patches, Simvastatin, Factorial designs, Matrix, Eudragit.

INTRODUCTION

The topical route of drugs has some limitations, so if not properly designed they have only local therapeutic effects. Transdermal patches containing drugs are the unique form of delivery of drugs for the entire surface of the skin. Skin is the largest organ of the body having a large surface area. It contains several layers and ultimately capillaries found just below the skin. Transdermal drug delivery has many advantages over drugs for oral route and parenteral. In drug toxicity and overdose, drugs can be easily withdrawn from the application site. Transdermal is the route which follows fully hepatic bypassing and hence reduces the degradation by hepatic enzymes. Another advantage associated with this is convenient to use appropriate for many hours or days. Such a type of useful dosage form usually increases patient compliances.[1] Transdermal drug delivery systems are applied on the skin that may deliver the medicament into the circulatory system of the body at a predefined rate. A transdermal drug delivery system is a different delivery system than the oral or parenteral drug delivery systems. In this system, the drug enters into the circulation directly via the skin by the diffusion process. A high concentration gradient of the drugs in a patch facilitates proper diffusion into the blood circulation. This maintains a constant and appropriate concentration of drug in the blood flow.[2]

Simvastatin is the drug used in the delivery system. It is an oral antilipemic agent

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which inhibits HMG-CoA reductase. It is used in the treatment of primary hypercholesterolemia and is effective in reducing total and LDL-cholesterol, plasma triglycerides, and apolipoprotein B.

MATERIALS AND METHODS

Materials

The drug was collected from Cadila Pharma. Ltd., Gujarat as a gift sample. All grades of Eudragit were obtained from Evonik Industries, Germany as a gift sample. Other chemicals and polymers collected were of analytical grades.

Methods

Formulation of Transdermal Patches

Transdermal patches were prepared by the solvent casting technique employing a mercury substrate. Eudragit ERL100 and ERS100 in different ratiosusing 2^3 factorial designs were used to prepare matrix-type transdermal patch as given in Tables 1 and 2. Simvastatin was taken as a drug in each formulation and dibutyl phthalate was used as plasticizer[3] in the two different ratios. DMSO (dimethyl sulphoxide) was used as a penetration enhancer in the formulations. A total of eight formulations were prepared and studied. After 24 hr the patches were cut into the required size. The composition of various patches was taken according to the 2-level factorial design. The desiccator is used for storing transdermal patches.

Table 1: Independent variables and levels.

Independent Variable	Level	
	Low (-1)	High(+1)
A(Polymer-ERL100:ERS100)	6:4	8:2
B(Plasticizer %w/w)	30	40
C(Penetration enhancer %w/w)	0.25	0.50

Table 2: 2- Level Factorial Design.

Std	Run	Fac. 1 polymer conc.	Fac. 2 plasticizer conc.	Fac.3 penetration Enhancer
3	1	-1.00	1.00	-1.00
2	2	1.00	-1.00	-1.00
7	3	-1.00	1.00	1.00
4	4	1.00	1.00	-1.00
1	5	-1.00	-1.00	-1.00
5	6	-1.00	-1.00	1.00
8	7	1.00	1.00	1.00
6	8	1.00	-1.00	1.00

Evaluation of physicochemical properties of Transdermal Patches

Thickness

The thicknesses of transdermal patches were determined by digital Vernier calipers of least count 0.001mm at different points and the average of all was computed.

Folding endurance

Folding endurance is the capability or strength of patches to withstand repeated folding at a single point. It is obtained as a maximum number of counts of folding of patches to retain its breakability.[4,5]

Uniformity of weight

Weight variation was obtained by weighing 20 sample patches and the average weight of the sample was then calculated. The insignificant deviation from average weight is the uniformity of weight.[4,5]

Percentage moisture content

The sample of prepared films was initially weighed properly and kept in a desiccator containing partially filled with calcium chloride at the base and kept for 24 h at room temperature. The fillms were weighed and the percentage moisture content was obtained as a ratio of a difference value between initial and final weight to final weight multiplied by 100.[6,8]

$$\% \text{ moisture content} = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \times 100$$

Percentage moisture uptake

Previously weighed patches were stored in a desiccator containing a saturated solution of potassium chloride to provide 80 % RH for 24 h at room temperature. The percentage of moisture uptake was calculated as the ratio of a difference value between final and initial weight to initial weight multiplied by 100.

$$\% \text{ moisture uptake} = \frac{\text{final weight} - \text{initial weight}}{\text{initial weight}} \times 100$$

Drug content determination

Ten patches were weighed separately and dissolved in 100 ml of methanol. The solution was filtered through a 0.45 μm filter before drug analysis. The drug content was estimated spectrophotometrically at λ_{max} of 238.9 nm.

Ex-vivo evaluation of transdermal patches

Permeation studies acrosshuman cadaver skin[6]

Preparation of human cadaver skin

Human cadaver skin obtained from Lala Lajpat Rai Medical College, Meerut, was dermatomed carefully and was washed with deionized water. The skin was then treated with a 5%w/v solution of EDTA (ethylene diamine tetra acetic acid) for 8 hr. The epidermis was removed from the dermis carefully with forceps. The epidermal side of the skin was again washed with deionized water and was spread over cellophane. The storage of the skin was done in a freezer until used. In the experiment, the skin was collected and soaked in a phosphate buffer solution for 1 hr. It was gently dried by blotting over filter paper. Before using the skin sample was examined with a microscope for any histological changes.

Simvastatin release from the patch was measured through human cadaver skin using a diffusion cell. The area of diffusion cell was 1.75cm^2 and the volume of the receptor compartment was 25 ml. The treated human cadaver skin was placed between the donor and receptor compartment. Simvastatin loaded patch with area 1 cm^2 was placed on the membrane surface which was sealed from the atmosphere with paraffin. The solution was filled as such in the receptor compartment to touch the dermal side of the skin. A magnetic stirrer was used for stirring the solution in the receptor compartment using a magnetic bead. During the experiment, the solution in the receptor side was kept at 37±1°C temperature. At different time intervals, the samples were withdrawn from the diffusion cell by using a pipette for up to 24 hr. The collected samples were analyzed for the drug permeated across the skin. Receptor volume was adjusted with an equal volume of buffer at each time interval.[9,10] The observations are listed in Table 3.

Stability Studies

Formulations were studied for stability studies. These selected formulations were studied for different parameters for 45 days. The storage temperature and relative humidity were kept at 40±2°C and 75±5 % respectively.[11,12]

RESULTS

Analysis of variance table with design summary of the obtained results are given in Table 4. Observations of the thickness of transdermal patches were given in Table 5. To evaluate the thickness of different transdermal patches, ANOVA for the selected factorial model was done and details are given in Table 6 and Figure 2. The Bar-graph of the thickness of the formulations is given in Figure 1.

The mathematical models eliciting the effects of the various factors and their interactions over the thickness of patches were:

Thickness =153.38+4.37 A+5.87 B+5.62 C-1.12 A B+1.63 A C+1.13 BC-0.88 A B C

Where, A=Polymer, B=Plasticizer, and C=Penetration enhancer.

Different folding endurance values of transdermal patches were given in Table 5 To evaluate the folding endurance, ANOVA for the selected factorial model

Table 3: Percent drug permeate from simvastatin patches across human cadaver skin.

Time (hr)	Percent drug permeated*							
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
1	6.44±0.24	5.45±0.18	5.83±0.126	5.85±0.283	6.02±0.314	5.69±0.2445	5.6±0.168	6.00±0.323
2	10.3±0.36	9.95±0.30	10.2±0.296	10.2±0.335	10.9±0.388	10.0±0.3156	10.3±0.258	10.8±0.463
3	13.3±0.42	12.8±0.45	13.9±0.325	11.9±0.532	14.1±0.613	13.5±0.462	14.9±0.39	14.3±0.686
4	151.4±0.60	17.9±0.56	16.6±0.432	16.8±0.724	17.7±0.695	16.8±0.677	17.6±0.467	17.6±0.754
5	16.7±0.68	22.1±0.76	21.2±0.58	21.1±0.651	20.6±0.735	20.3±0.585	20.5±0.459	20.2±0.708
6	23.2±0.73	26.7±0.83	26.8±0.655	25.8±0.845	25.6±0.792	24.0±0.757	24.2±0.647	24.1±0.838
7	26.5±0.75	29.8±0.80	30.1±0.745	29.1±0.882	31.5±0.839	28.8±0.783	28.4±0.715	27.8±0.873
8	30.4±0.87	304.7±0.56	33.2±0.783	31.8±0.768	34.6±0.812	30.6±0.747	32.0±0.688	30.9±0.858
9	33.3±0.65	33.04±0.78	37.1±0.868	35.5±0.802	38.7±0.926	33.4±0.583	36.0±0.764	33.8±0.802
10	35.5±0.82	39.6±0.86	40.8±0.983	38.8±0.967	40.9±0.783	37.1±0.738	38.9±0.887	36.6±0.960
11	39.3±0.94	43.04±0.82	43.8±0.957	41.9±0.945	44.7±0.868	41.2±0.955	42.4±0.984	40.5±1.057
12	43.8±1.24	44.5±1.04	45.1±1.19	43.4±1.27	46.0±0.985	43.8±1.21	46.1±1.06	45.4±1.345
24	67.5±1.84	70.1±2.14	69.4±1.76	68.08±2.45	71.3±1.85	67.7±2.37	68.8±2.23	70.7±2.54

* mean±S.D, *n*=3

Table 4: Design summary.

Name	Units	Obs	Analysis	Minimum	Maximum	Mean	Std. Dev.	Ratio
Thickness	µm	8	Factorial	140	170	153.37	10.2112	1.21429
weight variation	Mg	8	Factorial	24.5	26.8	25.65	0.84176	1.09388
folding endurance	-	8	Factorial	102	221	165.75	46.6836	2.16667
moisture uptake	%	8	Factorial	1.103	2.627	1.8328	0.50544	2.38169
moisture content	%	8	Factorial	1.42	3.66	2.2025	0.67635	2.57746
Drug Content	%	8	Factorial	85.45	95.68	91.52	3.2582	1.11972
Drug permeation	µm/ cm^2	8	Factorial	595.2	680.3	634.63	33.5609	1.14298

Table 5: Physicochemical evaluation of different formulations.[7]

Formulation code	Thickness (µm±SD)	Folding endurance	Weight variation (mg±SD)	Moisture uptake (%)	Moisture content (%)	Drug content (%)	Overall desirability
F1.	144±14.28	112.2±4.91	25±1.469	1.35±0.163	1.83±0.089	90.37±4.06	0.354
F2.	155±15.49	195±7.738	26.2±1.78	1.46±0.199	2.25±0.117	92.82±5.33	0.682
F3.	150±10.77	135±6.046	25.1±1.41	1.93±0.299	1.74±0.166	89.64±3.66	0.000
F4.	160±13.26	201±6.679	26.4±1.62	2.11±0.136	2.42±0.130	94.42±5.11	0.586
F5.	162±15	210±5.436	26.2±1.09	2.2±0.164	2.32±0.139	93.46±4.44	0.574
F6.	146±9.165	150±4.928	25±1.24	1.89±0.179	1.98±0.151	90.32±2.85	0.265
F7.	140±6.403	102±4.9	24.5±1.07	1.10±0.169	1.42±0.137	85.45±3.35	0.000
F8.	170±8.306	221±5.585	26.8±0.9	2.62±0.195	3.66±0.153	95.68±4.68	0.867

Table 6: Analysis of variance table [Partial sum of squares - Type III for thickness].

Source	Sum of Squares	D_f	Mean Square	*F* Value	*p*-value Prob > F
Model significant	682.37	3	227.46	19.15	0.0078
A-polymer	*153.12*	*1*	*153.12*	*12.89*	*0.0229*
B-plasticizer	*276.12*	*1*	*276.12*	*23.25*	*0.0085*
C-penetration enhancer	*253.12*	*1*	*253.12*	*21.32*	*0.0099*

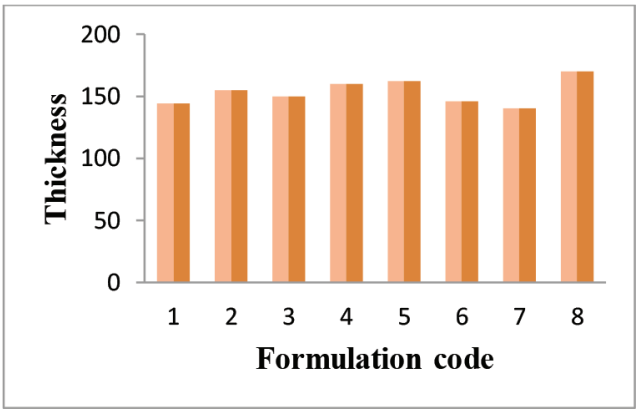

Figure 1: Thickness of different formulations.

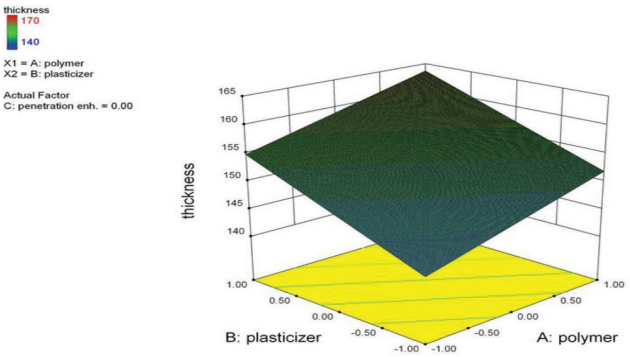

Figure 2: Thickness of patches as a function of: a) polymer, b) plasticizer.

was done and details are given in Figure 4 and graph of different formulations vs their respective folding endurance is given in Figure 3. The Bar-graph of folding endurance values of different formulations is reported in Figure 3.

Different weight variation observations of the patches were given in Table 5

To evaluate the weight variation of patches, ANOVA for the selected factorial model was done and details are given in Table 7 and Figure 6 and graph of different

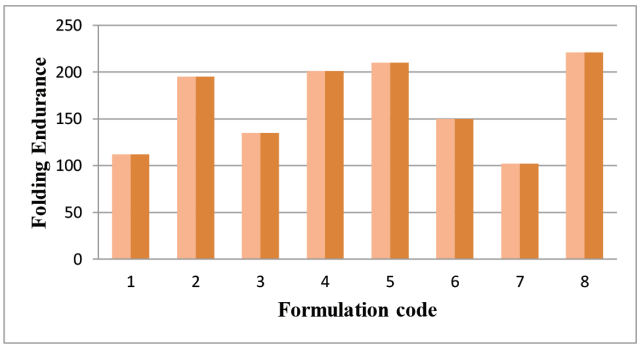

Figure 3: Folding endurance of different formulations.

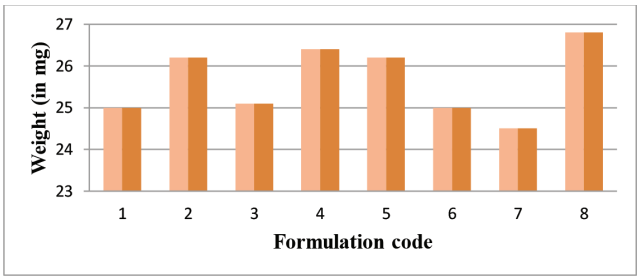

Figure 5: Weight variations of different formulations.

Table 7: Analysis of variance table [Partial sum of squares - Type III- for weight variation].

Source	Sum of Squares	D_f	Mean Square	*F* Value	*p*-value Prob > F
Model significant	4.68	3	1.56	22.72	0.0057
A-polymer	*1.62*	*1*	*1.62*	*23.56*	*0.0083*
B-plasticizer	*1.44*	*1*	*1.44*	*21.02*	*0.0101*
C-penetration enhancer	*1.62*	*1*	*1.62*	*23.56*	*0.0083*

Table 8: Analysis of variance table [Partial sum of squares - Type III for moisture content].

Source	Sum of Squares	D_f	Mean Square	*F* Value	*p*-value Prob > F
Model significant	2.81	3	0.94	9.44	0.0275
A-polymer	*1.12*	*1*	*1.12*	*11.36*	*0.0280*
B-plasticizer	*0.67*	*1*	*0.67*	*6.79*	*0.0596*
C-penetration enhancer	*1.01*	*1*	*1.01*	*10.18*	*0.0332*

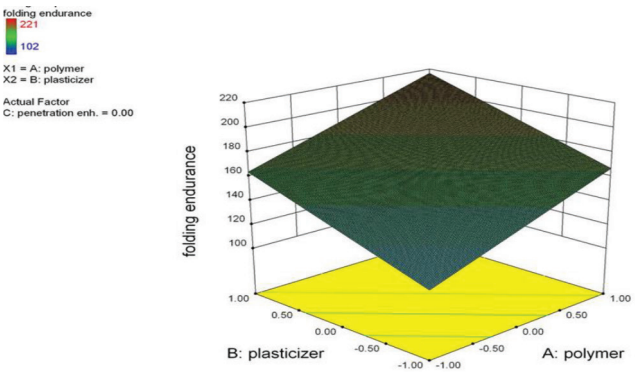

Figure 4: Folding endurance of patches as a function of a) polymer, b) plasticizer.

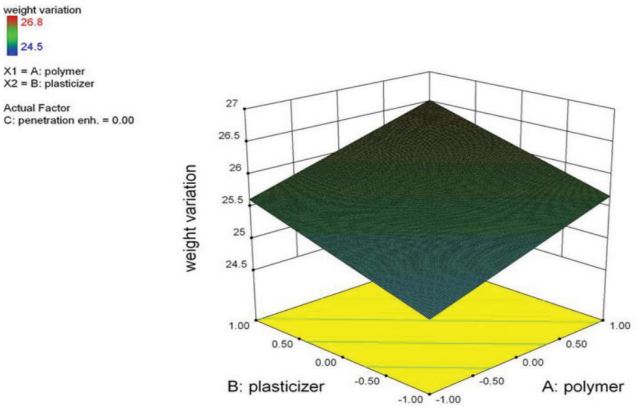

Figure 6: Weight variations of patches as a function of: a) polymer, b) plasticizer.

formulations vs their weight variations are given in Figure 5. The bar-graph of the weight variation of the formulations is given in Figure 5.

Different percent moisture content values of transdermal patches were given in Table 5. To evaluate the moisture content of patches, ANOVA for the selected factorial model was done and details are given in Table 8 and Figure 8. The bar-graph of different formulation vs their percent moisture content is given in Figure 7.

The mathematical models eliciting the effects of the various factors and their interactions over percentage moisture content of patches were:

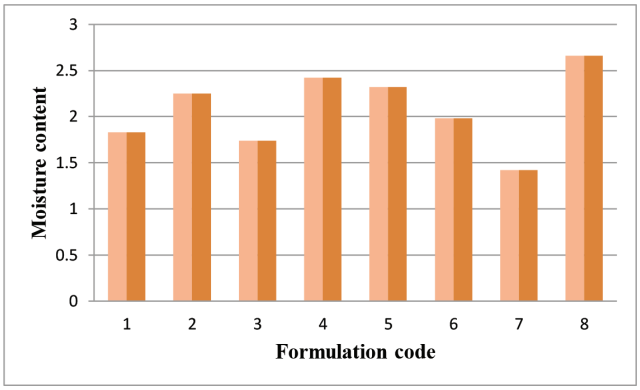

Figure 7: Moisture content of different formulations.

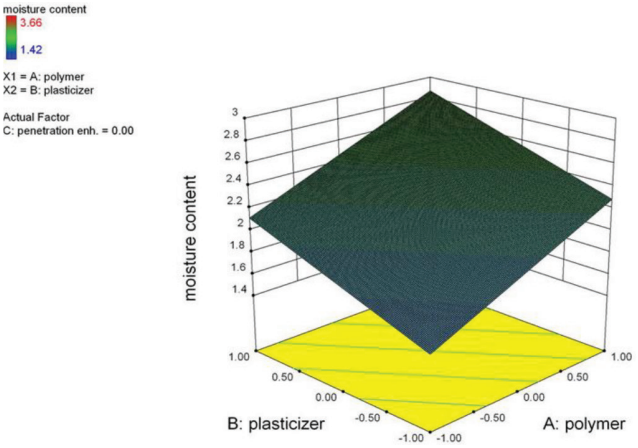

Figure 8: Moisture content of patches as a function of: a) polymer, b) plasticizer.

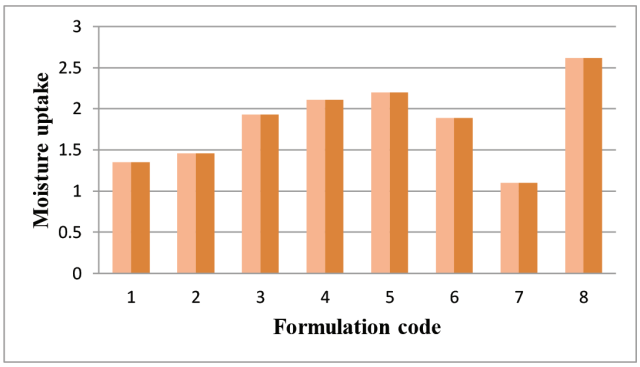

Figure 9: Moisture uptakes of different formulations.

Table 9: Analysis of variance table [Partial sum of squares - Type III- moisture uptake].

Source	Sum of Squares	D_f	Mean Square	*F* Value	*p*-value Prob > F
Model significant	1.14	3	0.38	2.34	0.2152
A-polymer	*0.30*	*1*	*0.30*	*1.85*	*0.2458*
B-plasticizer	*0.40*	*1*	*0.40*	*2.46*	*0.1917*
C-penetration enh	*0.44*	*1*	*0.44*	*2.70*	*0.1757*

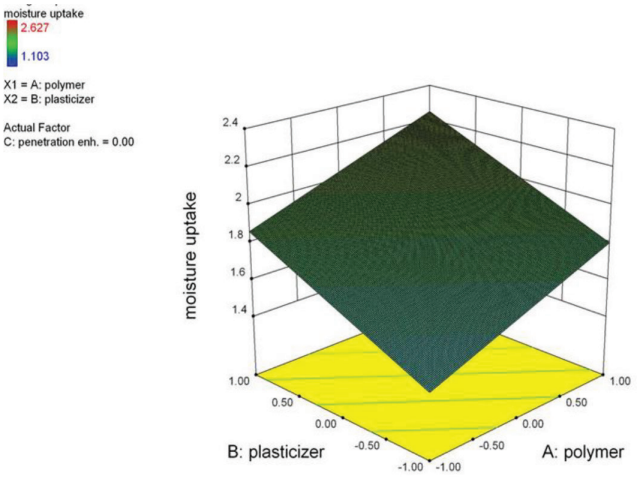

Figure 10: Moisture uptake of patches as a function of: a) polymer, b) plasticizer.

Moisture content = 2.20+0.38 A+0.29 B+0.36 C+0.087 A B+0.11 A C+0.14 BC+0.10 A B C

Where, A=Polymer, B=Plasticizer, and C=Penetration enhancer.

The mathematical models eliciting the effects of the various factors and their interactions over the weight variations of patches were:

Weight variation =25.65+0.45 A+0.42 B+0.45 C-0.025 A B+0.050 A C-0.025 B C-0.18 A B C

Where, A=Polymer, B=Plasticizer, andC=Penetration enhancer.

The results of percentage moisture uptake of different formulations were given in Table 5. For evaluating the percentage moisture uptake of patches, ANOVA for the selected factorial model was done and details are given in Table 9 and Figure 10. The bar-graph of different formulations vs their percent moisture uptake is given in Figure 9.

The mathematical models eliciting the effects of the various factors and their interactions over percentage moisture uptake of patches were:

Table 10: Analysis of variance table [Partial sum of squares - Type III for drug content].

Source	Sum of Squares	D_f	Mean Square	*F* Value	*p*-value Prob > F
Model significant	71.68	3	23.89	36.32	0.0023
A-polymer	*25.63*	*1*	*25.63*	*38.96*	*0.0034*
B-plasticizer	*15.24*	*1*	*15.24*	*23.16*	*0.0086*
C-penetration enh	*30.81*	*1*	*30.81*	*46.83*	*0.0024*

Moisture uptake =1.83+0.19 A+0.22 B+0.23 C-0.20 A B+0.11 A C+0.12 B C+0.11 A B C

Where, A=Polymer, B=Plasticizer, and C=Penetration enhancer.

Different drug content values of transdermal patches were given in Table 5. For evaluating the drug content of transdermal patches of different formulations, ANOVA for the selected factorial model was done and details are given in Table 10 and Figure 12. The bar-graph of dif-

ferent formulations vs their percent drug content is given in Figure 11.

The mathematical models eliciting the effects of the various factors and their interactions over drug content of patches were:

Drug content = 91.52+1.79 A+1.38 B+1.96 C-0.44 A B- 0.22 A C- 0.29 B C- 0.018 A B C

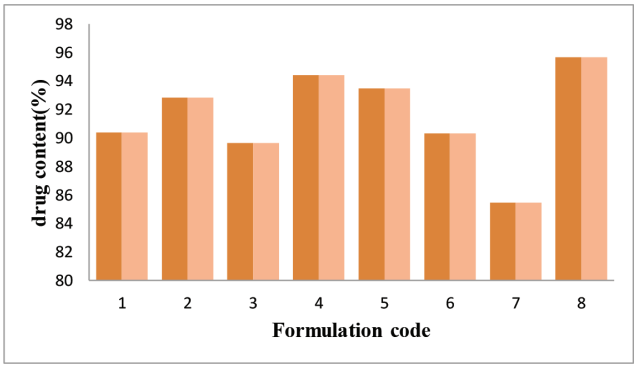

Figure 11: Drug content of different formulations.

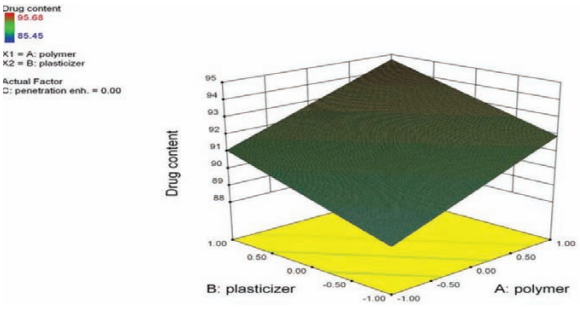

Figure 12: Drug content of patches as a function of: a) polymer, b) plasticizer.

Where, A=Polymer, B=Plasticizer, and C=Penetration enhancer.

The observations of drug permeation across human cadaver skin as the *ex-vivo* study was given in Table 11 and 12. ANOVA for the selected factorial model was done and details are given in Table 12 and Figure 14. Graph of Drug permeation (µg/cm^2) of different formulations vrs different formulations is given in Figures 13,15,16.

The mathematical models eliciting the effects of the various factors and their interactions over the thickness of patch were:

Drug permeation = 633.10+15.50 A+15.22 B+15.08 C-4.53 A B-4.57 A C+5.14 B C-2.16 A B C.

In the design, the three factors were A=Polymer, B=Plasticizer, and C=Penetration enhancer.

DISCUSSION

Drug compatibility study with all polymers showed no interaction between drug and polymers. The estimated partition coefficient of the drug indicates that the drug has adequate lipophilic characteristics suitable for transdermal patches. Simvastatin containing patches were evaluated for various parameters of transdermal patches including *ex-vivo* permeation study. Drug content study indicated homogeneous drug distribution in the film and other physicochemical properties were found to be optimum.[13,14]

Formulation F8 has the highest values ofpermeation parameters like flux, amount of drug permeated, and permeability coefficient. Based on all parameters,

Table 11: Cumulative drug permeate (µg/cm^2) from simvastatin patches.[7,8]

Time	Drug permeated (µg/cm^2) *							
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
1	58.2±2.486	50.32±1.885	52.3±2.126	55.76±2.83	56.32±3.14	53.67±2.445	48.55±1.68	57.32±3.234
2	93.4±3.624	91.65±3.02	91.42±2.96	96.4±3.356	102.6±3.88	93.56±3.156	88.89±2.58	103.43±4.63
3	120.2±4.29	118.4±4.58	124.3±3.25	112.2±5.32	131.3±6.13	125.66±4.62	127.22±3.9	136.33±6.86
4	151.4±6.02	165.8±5.62	148.6±4.32	158.2±7.24	165.3±6.95	158.87±6.77	150.5±4.67	168.87±7.54
5	178.1±6.89	204.5±7.67	187.32±5.8	198.5±6.51	192.5±7.35	189.7±5.85	175.2±4.59	192.32±7.08
6	210.2±7.33	246.9±8.32	239.4±6.55	243.8±8.45	239.4±7.92	224.4±7.57	206.4±6.47	229.34±8.38
7	240.3±7.59	275.8±8.06	268.5±7.45	274.3±8.82	293.5±8.39	268.4±7.83	242.4±7.15	264.2±8.73
8	275.6±8.73	304.7±5.68	296.5±7.83	299.2±7.68	322.6±8.12	285.4±7.47	272.5±6.88	294.2±8.58
9	301.2±6.58	340.5±7.83	330.5±8.68	334.3±8.02	360.4±9.26	311.3±5.83	306.3±7.64	322.3±8.02
10	320.2±8.22	365.3±8.67	364.6±9.83	365.5±9.67	381.7±7.83	345.4±7.38	331.3±8.87	348.5±9.60
11	355.2±9.47	396.6±8.28	390.3±9.57	394.3±9.45	416.4±8.68	384.5±9.55	361.2±9.84	385.4±10.57
12	396.6±12.4	410.2±10.4	402.4±11.9	408.4±12.7	428.5±9.85	408.4±12.1	392.3±10.6	432.3±13.45
24	610.2±18.4	645.8±21.4	618.4±17.6	640.6±24.5	664.6±18.5	630.7±23.7	585.6±22.3	672.2±25.4

* mean±S.D, *n*=3

Table 12: Analysis of variance table [partial sum of squares - Type III for drug permeation].

Source	Sum of Squares	Df	Mean Square	*F* Value	*p*-value Prob > F
Model significant	5593.54	3	1864.51	12.85	0.0160
A-polymer	*1922.31*	*1*	*1922.31*	*13.25*	*0.0220*
B-plasticizer	*1852.88*	*1*	*1852.88*	*12.77*	*0.0233*
C-penetration enhancer	*1818.35*	*1*	*1818.35*	*12.53*	*0.0240*

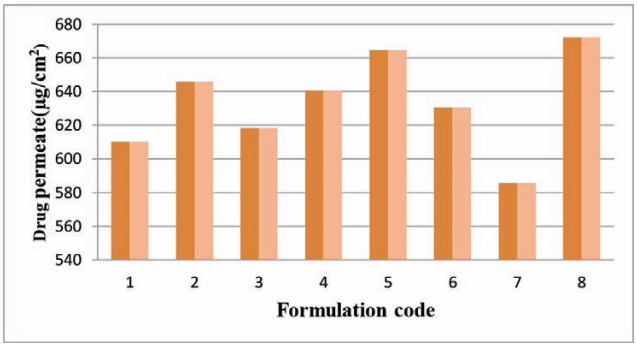

Figure 13: Drug permeation of different formulations.

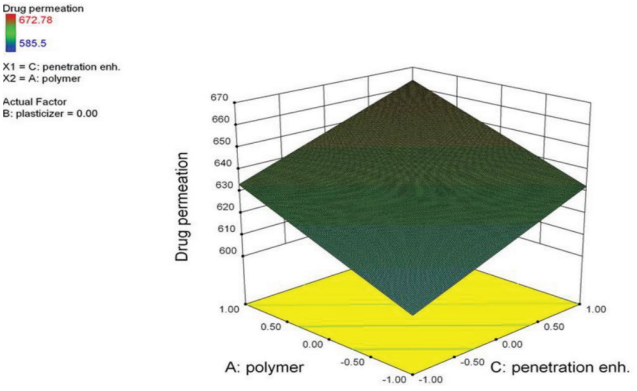

Figure 14: Drug permeation of patches as a function of: a) polymer, b) penetration enhancer.

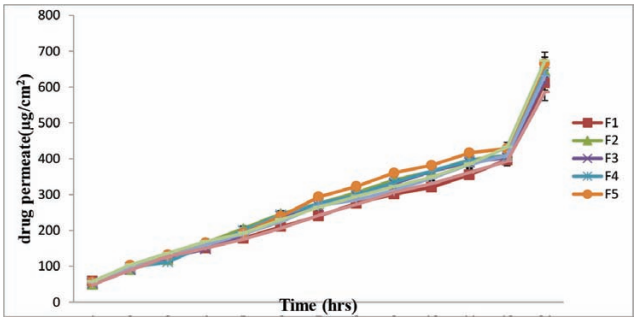

Figure 15: Amount of drug permeated from different patches.

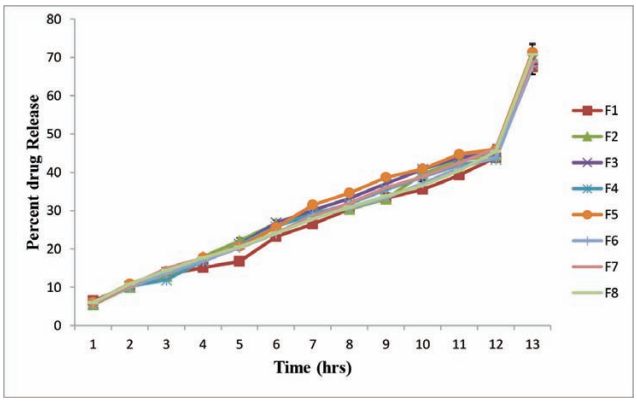

Figure 16: Percent drug permeation from different patch formulations.

formulation F8 was considered as the best formulation. The films were subjected to stability studies at 45°C and 75% RH for 45 days and were found stable with respect to their physicochemical parameters, drug permeation, and flux value.

CONCLUSION

Simvastatin was found compatible with all polymers and excipients used for the formulations. The estimated partition coefficient of the drug indicates that the drug possesses sufficient lipophilicity which meets the requirements of a transdermal patch. It may be a promising delivery system for the treatment of primary hypercholesterolemia.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

DMSO: Dimethyl Sulphoxide; **RH:** Relative Humidity; **h:** Hour; µm: Micrometer; **w/v:** weight/volume; **EDTA:** Ethylene Diamine Tetraacetic Acid; **SD:** Standard Deviation; **Df:** Degree of freedom.

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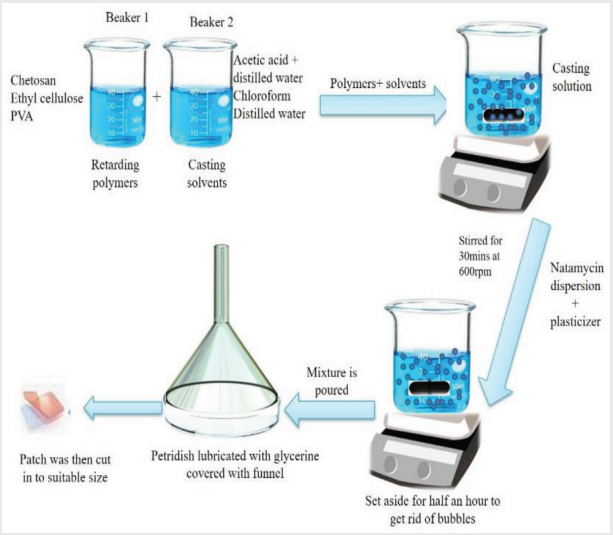
PICTORIAL ABSTRACT



SUMMARY

- Simvastatin-containing patches were evaluated for weight variation, thickness, folding endurance, percentage moisture uptake, percentage moisture content, drug content, and *ex-vivo* permeation study. Drug content study indicated homogeneous drug distribution in the film and other physicochemical properties were found to be optimum.
- The permeation parameters like flux, amount of drug permeated, and permeability coefficient were found highest for formulation F8, based on all parameters, formulation F8 was considered as the best formulation. The films were subjected to stability studies at 45°C and 75% RH for 45 days and were found stable concerning their physicochemical parameters, drug permeation, and flux value.

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