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DEVELOPMENT AND EVALUATION OF MATRIX TYPE TRANSDERMAL PATCHES OF SIMVASTATIN

Aftaab, Aparna Joshi, Kapil Kumar, Vaishali Chauhan, Ikram, Vaishali Rajput
Division of Pharmaceutics, Global Institute of Pharmaceutical Education and Research, Kashipur, Uttarakhand

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Abstract

Transdermal patches are a cutting-edge drug delivery technology, as it avoids first-pass metabolism results in increased bioavailability and aid in the delivery of drug molecules into the systemic circulation at predetermined and controlled rate. Aim behind this invention was to formulate a stable, reproducible and non-infringing & examine matrix-type transdermal patches of Simvastatin by using solvent evaporation method and the formulation consist various polymer including HPMC, Ethyl Cellulose, Chitosan, PVPK-30 and Eudragit RS 100, plasticizers like glycerine, propylene glycol, and trietholamine are utilised, along with solvents like octanol and ethanol. The prepared 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 P4 showed better characteristic properties and in vitro drug diffusion.

Keywords: Transdermal drug delivery system, Simvastatin, HPMC, Eudragit RS100, Ethyl Cellulose.

***Corresponding Author**
Vaishali Rajput

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Introduction

Transdermal drug delivery system 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. 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 [1]. In TDDS, systemic absorption of drugs achieved by overcoming the hurdles related to API Characteristics like molecular size, lipophilicity, permeability, with aid of physical or chemical enhancers. Transdermal drug delivery had become an appealing and patience acceptance technology as it is minimize and avoids the limitations allied with conventional as well as parenteral route of drug administration and has higher number of advantages over the oral route of administration [2].

It includes the non-invasive delivery of medications from the surface of skin-the largest and most accessible organ of human body- through its layers, to the circulatory system. A transdermal patch is defined as medicated adhesive patch which is placed above the skin to deliver a specific dose of medication through the skin with a predetermined rate of release to absorb into the bloodstream through follicular and intercellular route by diffusion process [3].

There is considerable interest in the skin (comprises three distinct layers- cellular epidermis, dermis and hypodermis) as a site of drug application both for local and systemic effect because skin is a readily accessible surface for drug delivery and it covers a surface of approximately 2m2 of adult body and receives about one-third of the blood circulating through the body [4].

Basically, transdermal devices contain therapeutically active ingredients, polymer matrix which controls the release of the drug from the device, permeation enhancer to increase permeability of drug candidate, adhesives to maintain an intimate contact between transdermal system and the skin surface, a backing layer and other excipients [5].

Simvastatin is HMG-CoA reductase inhibitor and acts as an anti-hyperlipidemic drug. It is lipophilic in nature, the plasma half-life of simvastatin is 2h with an oral

bioavailability of 5% [6]. Simvastatin is an ideal candidate for the preparation of transdermal films as it has low molecular weight (418.56 g/mol), high lipid solubility, low melting point (129 °C), effective in low plasma concentration as well as a high degree of first-pass metabolism [7,8].

Materials and Methods

Materials

Simvastatin was a gift sample from Mylan laboratories ltd, Eudragit RS 100 was a gift sample from Asia private ltd, Triethanolamine, SLS, Di-sodium hydrogen phosphate, ethanol, HCl, Potassium di-hydrogen orthophosphate, NaOH pellets, propylene glycol, Glycerine, PVPK-30 were from Central Drug House, Delhi and chitosan was gift sample from Central Institute of Fisheries, Cochin, HPMC K100 M was gift sample from Cipla, Mumbai & Ethyl cellulose was gift sample from Asia private ltd. (Goa).

Formulation development

General procedure for fabricating the drug free films

A fixed volume of polymer solution with plasticizer was poured onto a glass petri dish of inner diameter 8.5 cm and height 2 cm. The Petri dish was placed on oven and smooth surface to ensure uniform spreading of the polymer solution. An inverted funnel was placed on the Petri dish to control the rate of evaporation of the solvent at the controlled rate over the drying periods of 12 hrs at 40 °C. The film thus formed was retrieved by cutting along the edges with a sharp razor blade9.10.

General Procedure for fabricating the Simvastatin loaded polymeric films

The compositions of the patches are shown in table-6. The drug loaded polymeric films were prepared in a similar manner described above except that a weighed quantity of the drug Simvastatin was dissolved to the polymer solution containing the plasticizer. This solution was poured into a glass petri dish. An inverted funnel was placed on it to control the rate of evaporation. The whole assembly was maintained at 40°C in hot air oven. At the end of the 12 hrs the film was lifted from the surface of Petridish after the cutting the edges with a sharp razor. The film thus formed was neutralized with 2 % NaOH and dried. After that the film was isolated and wrapped in an aluminium foil and stored at 79.5 % relative humidity chamber (desiccator) containing solution of ammonium chloride until further use [11].

Evaluation

The prepared transdermal patches were evaluated in terms of the physical properties, *in-vitro* release. For the evaluation of the patches a particular number of the patches were selected in order to find out the standard deviation to check the versatility of the results in the batches.

Physical Properties

1. Thickness: The thickness of each film was measured at five different places by means of a screw gauge12.

2. Weight Uniformity: Five patches of each film were weighed accurately and the average weight of the patch was found out [13].

3. Content Uniformity: To determine the amount of Simvastatin in the patches, the patch of was dissolved in 10ml of phosphate buffer solution (pH 7.4) and then after dilution the amount was measured spectrophotometrically at 232 nm [14].

4. Folding Endurance: The folding endurance of the patch was determined by repeatedly folding one patch at the same place up to 290 times, which was considered satisfactory to reveal good patch properties15.

The number of times the patch could be folded at the same place without breaking gave the value of folding endurance.

5. Percentage moisture loss: The films were weighted accurately and kept in a desiccators containing anhydrous calcium chloride. After 3 days, the films were taken out and weighed. The moisture loss was calculated using the formula [16].

$$\%\ \text{Moisture loss} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} X100$$

6. Percentage moisture content: The prepared films were weighed individually and kept in a desiccator containing silica at room temperature and the films were weighed again and again until they showed a constant weight. The percentage moisture content was calculated using the following formula [17].

$$\%\ \text{Moisture content} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} X100$$

7. Percentage moisture absorption: The films were weighed accurately and placed in the desiccator containing 100 ml of saturated solution of aluminium chloride which maintains 79.50% RH. After 3 days the films were taken out and weighed. The percentage moisture absorption was calculated using the formula18.

$$\%\ \text{Moisture absorption} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Initial Weight}} X100$$

8. Water vapour transmission rate: For this study vials of equal diameter were used as transmission cells. These cells were washed thoroughly and dried in an oven. About 1.0g of fused calcium chloride was taken in the cells and the polymeric films were fixed over the brim with the help of an adhesive. The cells were weighed accurately and initial weight is recorded and then kept in a closed desiccator containing saturated solution of potassium chloride (200ml), containing humidity between 80-90% RH. The cells were taken out and weighed after 1, 2, 3, 4, 5, 6, and 7th day of storage19. From increase in the weights the amount of water vapour transmitted and rate at which water vapour transmitted were calculated as shown below.

$$\text{WVTR} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Time x Area}} X100$$

9. Flatness: Longitudinal strips of 1.6 cm in length were cut out from the prepared medicated film and then

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variation in the lengths due to the non-uniformity in flatness was measured [20].

Flatness was calculated by measuring constriction of strips and a zero percent constriction was considered to be equal to a hundred percent flatness.

$$\text{Constriction (\%)} = \frac{l1 - l2}{l2} X100$$

Where, l1 = final length of each strip, and l2 = initial length

10. In-vitro release studies: A modified Franz-diffusion cell was fabricated to study the *in-vitro* release. The diffusion cell consists of two cylindrical compartments in vertical arrangement, a donor compartment which was exposed to ambient temperature and a receptor compartment, which was maintained at 370C. The receptor compartment has a sampling port for removing samples at different time intervals. The two compartments were held together with the help of rubber bands. The solution hydrodynamics in the receptor compartment was kept constant by the rotation of the magnetic bead. For the in-vitro study the patches were stuck to an aluminum foil which was previously cut to have a diameter of 2 cm and a slightly larger patch was fixed using water-impermeable adhesive to ensure that the receptor fluid does not come in contact with the sides of the films. Before placing the patch fixed on to the diffusion cell, the mouth of the cell was coated with a thin layer of silicone grease to prevent leakage of the receptor fluid 1 ml of the receptor fluid was withdrawn at periodic interval for 10 hrs. It was immediately replaced with 1 ml of fresh drug free buffer (pH 5.0) solution to maintain constant volume. The fluid removed, after suitable dilution with phosphate buffer was analyzed spectrophotometrically at 232 nm [21-24].

Drug release kinetic data analysis:

The release data obtained from various formulations is studied for their fitness of data in different kinetic models like first order and Peppa's. PCP disso Version 2 software was used in this study [25, 26].

1. First order kinetics:

Release rate = k [A] ..... (1)

A is concentration of reactant

2. Korsemeyer, s and Peppas release model:

$$Mt / M\infty = K.tn \quad \ldots\ldots (2)$$

Where, Mt / M∞ = fraction of drug release, K = release constant, t = release time, n = Diffusion exponent for the drug release that is dependent on the slop of the matrix dosage forms.

12: Stability study: Stability studies carried out by storing the prepared transdermal patches of selected batches MTP1 and MTP5 at various temperature conditions like refrigeration on (2-80C) room temperature (25±0.50C) and elevated temperature (45±0.50C) for a period of 12 weeks. Drug content and variation in the average vesicle diameter were periodically monitored. ICH (International Conference on Harmonisation) guidelines were followed [27].

Results

Table 7: Compositions of the Simvastatin transdermal patches.

Batch Code	Simvastatin (mg)	Polymer Ratio	Solvent (w/v)	Plasticizer
P1	300	Chitosan: PVP K30::20:80	Acetic acid(1%)	Propylene glycol (30%)
P2	300	Chitosan: PVP K30::40:60	Acetic acid(1%)	Propylene glycol (30%)
P3	300	Chitosan: PVP K30::60:40	Acetic acid(1%)	Propylene glycol (30%)
P4	300	Chitosan: PVP K30::80:20	Acetic acid(1%)	Dibutylphthalate (30%)
P5	300	Chitosan :Ethyl cellulose:: 20:80	Acetic acid(1%)	Dibutylphthalate (30%)
P6	300	Chitosan :Ethyl cellulose:: 40:60	Acetic acid(1%)	Dibutylphthalate (30%)
P7	300	Chitosan :Ethyl cellulose:: 60:40	Acetic acid(1 %)	Glycerine (20%)
P8	300	Chitosan :Ethyl cellulose:: 80:20	Dichloromethane (2%)	Propylene glycol (30%)
P9	300	HPMC:PVP K30::20:80	Dichloromethane (2%)	Castor oil (20%)
P10	300	HPMC:PVP K30::40:60	Dichloromethane (2%)	Propylene glycol (30%)

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Table 8: Characterization of matrix type transdermal patches of Simvastatin.

Batch Code	Physical Appearance	Thickness (mm) ± SD	Mass Uniformity (mg)	% Drug Content	% Moisture Content
P1	Smooth flexible but wrinkled	0.043 ± 0.09	48.6 ± 0.09	96.62± 0.12	3.53 ± 0.64
P2	Smooth tough	0.039 ± 0.18	45.4 ± 0.15	95.79± 0.12	3.34 ± 0.65
P3	Smooth flexible but wrinkled	0.042 ±0.31	46.1 ± 0.18	94.65± 0.12	3.68 ± 0.21
P4	Hard and tough	0.053 ± 0.09	43.2 ± 0.23	95.31± 0.15	3.45 ± 0.24
P5	Smooth tough	0.038 ± 0.19	46.7 ± 0.11	96.31± 0.32	2.55 ± 0.16
P6	Smooth tough	0.039 ± 0.41	45.5 ± 0.12	94.42± 0.12	2.75 ± 0.09
P7	Smooth tough	0.036 ± 0.09	44.3 ± 0.08	98.42± 0.09	2.79 ± 0.16
P8	Smooth flexible but wrinkled	0.042 ± 0.21	46.7 ± 0.08	95.42± 0.09	2.89 ± 0.16
P9	Smooth tough	0.039 ± 0.08	47.9 ± 0.11	94.52± 0.21	2.75 ± 0.13
P10	Smooth flexible but wrinkled	0.038 ± 0.19	46.7 ± 0.14	97.35± 0.32	2.65 ± 0.15

Table 9: Characterization of matrix type transdermal patches of Simvastatin-2.

Batch Code	% Moisture Absorption	% Moisture loss	WVTR (g/cm2/hrs	Folding Endurance	Flatness
P1	7.208 ± 0.21	3.659 ± 0.09	1.558X10-4 ± 0.14	> 257	100%
P2	6.331 ± 0.32	3.745 ± 0.08	1.771X10-4 ± 0.21	> 272	100%
P3	8.232 ± 0.41	3.739 ± 0.14	1.662X10-4 ± 0.09	> 267	100%
P4	8.408 ± 0.09	3.659 ± 0.21	1.458X10-4 ± 0.21	> 270	100%
P5	7.684 ± 0.11	3.731 ± 0.12	1.732X10 -4± 0.11	> 267	100%
P6	6.542 ± 0.07	2.781± 0.09	2.427X10-4± 0.11	> 264	100%
P7	5.428 ± 0.89	3.552 ± 0.08	2.528 X10-4± 0.13	> 245	100%
P8	4.455 ± 0.09	2.724 ± 0.11	2.731X10-4±0.14	> 274	100%
P9	5.582 ± 0.11	3.432 ± 0.12	2.847X10-4± 0.09	> 288	100%
P10	6.884 ± 0.09	3.531 ± 0.14	2.732X10 -4± 0.08	> 275	100%

mean ± SD, N=3

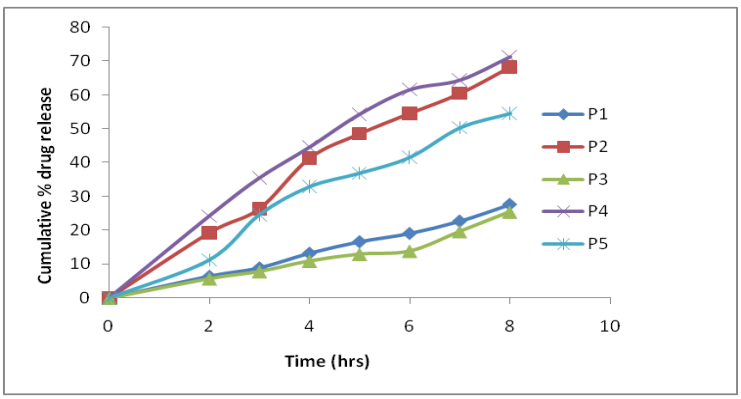

Figure 6: Percentage of drug released from Simvastatin transdermal patches of batch P1 to P5.

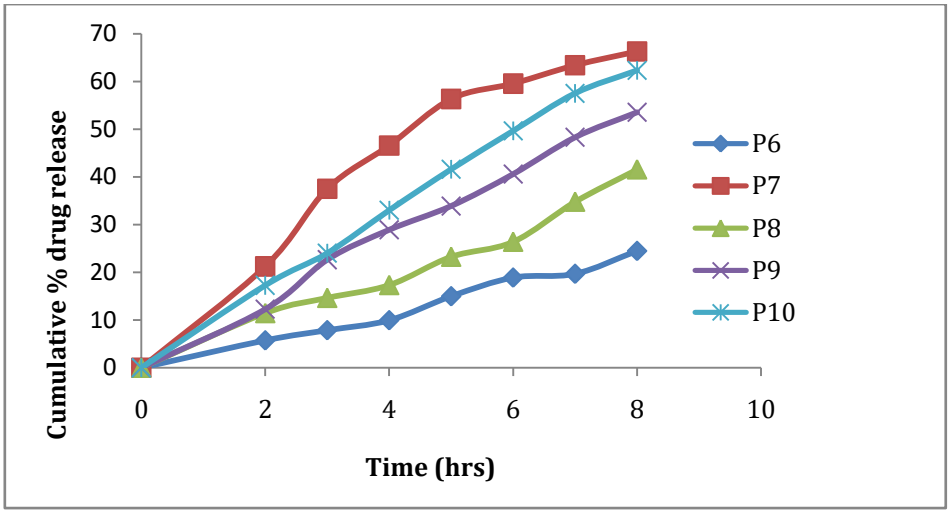

Figure 7: Percentage of drug released from Simvastatin transdermal patches of batch P6 to P10.

Table 12: *In-vitro* release kinetics of different Simvastatin transdermal patches.

Batch Code	Kinetic model	Parameters
P1	First order	R = 0.964, K1 = 3.177, n = 0.864
P2	Peppas and Korsmeyer	R = 0.962 , K1 = 7.642, n = 0.732
P3	Peppas and Korsmeyer	R = 0.961, K1 = 7.442, n = 0.762
P4	First order	R = 0.972, K1 = 5.61, n = 0.760
P5	Peppas and Korsmeyer	R = 0.974, K1= -0.070
P6	Peppas and Korsmeyer	R = 0.984, K1 = 5.2154, n = 0.864
P7	Peppas and Korsmeyer	R = 0.943, K1 = 6.712, n = 0.782
P8	Peppas and Korsmeyer	R = 0.975, K1 = 4.284, n = 0.760
P9	Peppas and Korsmeyer	R = 0.983, K1 = 8.243, n = 0.718
P10	Peppas and Korsmeyer	R = 0.965, K1 = -0.034

Table 13: Stability studies of Simvastatin transdermal patches of batch MTP1 and P2.

Weeks	**Batch P2** (Mean±S.D, N=5)			**P4** (Mean±S.D, N=5)		
	Refrigeration	**Room**	**Oven**	**Refrigeration**	**Room**	**Oven**
0	100	100	100	100	100	100
1	99.86±0.03	99.87±0.03	98.74±0.02	99.83±0.03	99.89±0.02	98.82±0.03
3	99.84±0.05	99.77±0.04	97.53±0.05	99.72±0.07	99.84±0.06	97.93±0.06
6	99.77±0.06	99.78±0.07	97.48±0.06	99.88±0.08	99.78±0.07	97.73±0.05
9	99.69±0.02	99.74±0.01	97.34±0.08	99.65±0.09	99.72±0.09	97.34±0.02
12	99.64±0.04	99.65±0.08	96.72±0.09	99.51±0.04	99.69±0.07	97.21±0.08

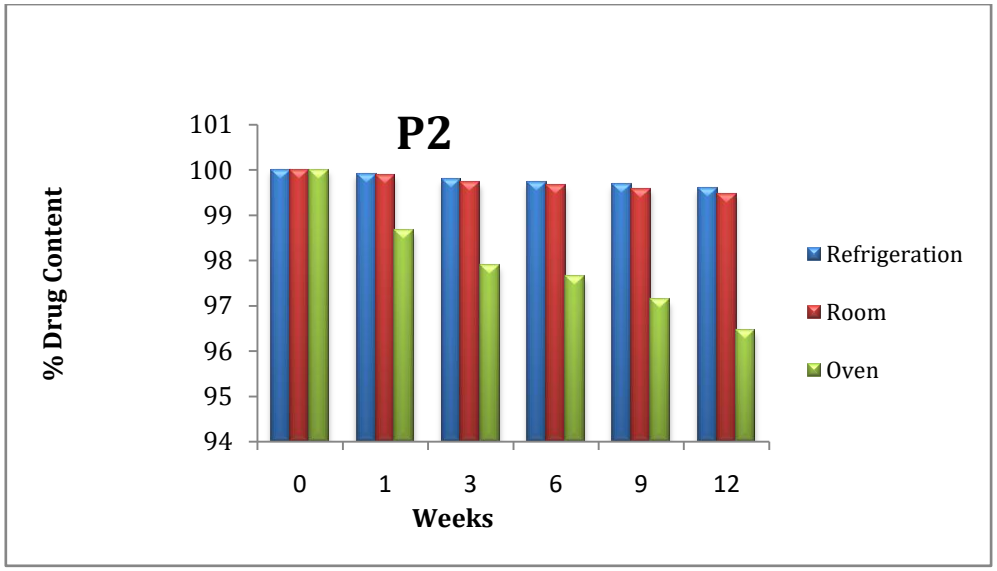

Figure 8: Stability study of Simvastatin transdermal patches of batch P2 at different temperature.

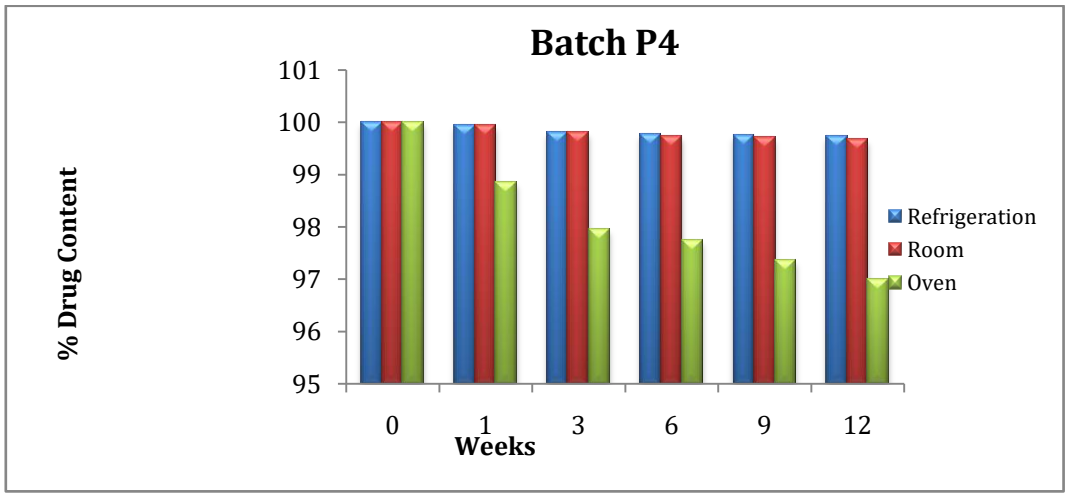

Figure 9: Stability study of Simvastatin transdermal patches of batch P4 at different temperature.

Results and Discussion

Development and evaluation of formulations

Twelve matrix type transdermal patches formulations of Simvastatin were prepared by using different polymers i.e. HPMC, chitosan, PVP K30, EC, in different ratio.

Thickness, weight uniformity and % drug content

The weight of patches lies in the range of 43.2 ± 0.23 to 47.9 ± 0.11 mg. The % drug content analysis of prepared formulations has shown that the process employed to prepare the study of the patches, was capable of giving uniform drug content and minimum batch variability.

Thickness lies in the range of 0.036 ± 0.09 to 0.053 ± 0.09 mm. Though the average thickness were almost uniform within same formulation a small variation in thickness was observed with different formulations. The variations in thickness may be attributed to viscosity of polymer solutions of different formulations. The other reasons may be due to lack of temperature control which have affected the controlled evaporation of solvent from the wet film surface. An increase or decrease in thickness had a direct relationship with weight of the patch and drug content. The % drug content lies in the range of 94.52± 0.21 to 98.42± 0.09. Content uniformity studies proved that the amount of Simvastatin in each patch of 2.009 cm2 was found to be fairly uniform containing 13-15 mg of Simvastatin.

% Moisture loss (% ML), % moisture content (% MC), % moisture absorption (% MA), water vapour transmission rate (WVTR)

WVTR was found is maximum in batch code P4 i.e. 2.847X10-4± 0.09 and minimum in formulations of batch code P9 i.e. 1.458X10-4 ± 0.21. % MA was found to be in the range of 4.455 ± 0.09 to 8.408 ± 0.09, largest in formulations of batch code P4 and least in the batch code P8. % MC was found to be in the range of 2.55 ± 0.16 to 3.68 ± 0.21, largest in batch code P3 and least in batch code P5. % ML was found to be in the range of 2.724 ± 0.11 to 3.745 ± 0.08 largest in batch code P2 and least in formulations of batch code P8.

Folding endurance- The folding endurance was measured manually; films were folded 290 times and if the

films shows any cracks it was taken as the end point. It was found maximum in formulation of batch code P9 (>288) and least in P7(>245).

The folding endurance represents the elasticity of the patches.

***In-vitro* drug release**

The in-vitro permeation of Simvastatin transdermal patches formulation was studied using locally fabricated Franz diffusion cell for 7 hrs. Largest in batch code P4 (71.28±0.19) and least in formulations of batch code P6(24.47±0.04). Rapid drug leakage was observed during the initial phase. However, after that a slow release occurred. It was also observed that the drug release generally decreased as the polymer ratio increased. The release of the drug was retarded due to the hydrophobic and insoluble nature of the polymers used. These results indicates hydrophilic nature of polymer PVP K30. Chitosan are more hydrophilic as compared to others. Hydrophobic polymer have less affinity for water this results in decrease in thermodynamic activity of the drug in the film and decreased drug release. The drug release was found to increase on increasing the concentration of hydrophilic polymer in the polymer matrix. This is due to the facts that dissolution of the aqueous soluble fraction of the polymer matrix leads to the formation of gelaneous pores. The formation of such pores leads to a decrease in the mean diffusional path length of the drug molecules to release into the diffusion medium and hence to higher release rates.

Kinetic modeling for transdermal patches PCP disso Version 2 software was used in this study. The results obtained in the in-vitro drug release studies were plotted in two models i.e. first order kinetic model, and Korsemeyer, s and Peppas release model. This indicates that the drug release is controlled by diffusion of the drug through the pores. The 'n' values of these indicate that in these formulations followed Fickian controlled release mechanism and in addition, the release appears to be also by erosion and is drug - dissolution limited. The selection criterion for the best model was based on goodness of fit and residual sum of squares.

Stability study: Accelerated stability studies for 12 weeks shows that the selected transdermal patches of batches P2 and P4 are capable to be stable at 450C as well as at refrigeration temperature. Therefore, the formulations may be kept at room temperature without affecting the properties.

Conclusion

Present study concludes successful delivery of the simvastatin is possible by the means of matrix type transdermal patches. Simvastatin transdermal patches formulations of batch P4 was concluded as the best formulations among the all 10 formulations based on different parameters like percentage drug content, percentage moisture content, moisture loss, folding endurance, *in-vitro* release and stability studies.

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Conflict Of Interest Statement

No conflict of interest.

Ethics Approval and Consent to Participate

Not applicable.

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