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Formulation and Evaluation of a Transdermal Drug Delivery System of Antihyperlipidemic Drug Simvastatin

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ABSTRACT

The present study was aimed at developing Simvastatin loaded transdermal patch to prevent drawbacks associated with oral delivery of Simvastatin. Simvastatin is a BCS class II drug having poor aqueous solubility and good permeability. A transdermal patch of simvastatin was developed using various polymers and their combination like Eudragit RL 100, HPMC K4M, PVP K30 & Ethyl Cellulose. Polymer combination HPMC K4M & PVP K30 exhibited good film forming properties. Propylene glycol, oleic acid and glycerol were used as plasticizers to improve film-forming properties. Among these, propylene glycol exhibited excellent result but penetration was found to be less. Thus, penetration enhancers such as oleic acid, DMSO, PEG 200 were used to enhance permeability, of which DMSO was found to be excellent. A 2^2 factorial design was implemented using design expert software. The formulation was optimized on basis of 2 parameters percent cumulative release and percent drug content. 3D surface graph was plotted for the design. Grid survey indicated P1 batch (which contains HPMC K4M & PVP K30 as a polymer, DMSO as penetration enhancer & PEG as a plasticizer) is the optimized batch as it showed good drug content and in-vitro drug release. The drug release kinetics of transdermal patch of simvastatin was best expressed by Higuchi model of drug release.

Keywords: Transdermal patch, Simvastatin, Hydroxy propyl methylcellulose K4M, Pyrolidone (PVP) K30, Dimethylsulphoxide(DMSO).

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INTRODUCTION

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the blood stream. Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drug via the skin to the systemic circulation. Moreover it over comes the various side effects like painful drug delivery and the first pass metabolism of the drug occurred by the means of drug delivery systems[1]. Transdermal delivery system bypass the hepatic first pass metabolism and avoid drug degradation due to gastrointestinal pH, enzymes etc., minimize plasma level fluctuations and extend the drug activity besides improving patient compliance[2]. Transdermal drug delivery systems (TDDS), also known as transdermal patches, are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. In order to deliver therapeutic agents through the human skin for systemic effects, the comprehensive morphological, biophysical and physicochemical properties of the skin are to be considered. Transdermal delivery provides a leading edge over injectable and oral routes by increasing patient compliance and avoiding first pass metabolism respectively[3]. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-life and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects[4,5]. Simvastatin mainly used for the treatment of hypercholesterolemia. In the blood, statins lower total and LDL cholesterol as well as triglycerides. LDL cholesterol is believed to be an important cause of coronary artery disease. Lowering LDL cholesterol levels slows and may even reverse coronary artery disease. Statins also increase HDL cholesterol. Raising HDL cholesterol levels, like lowering LDL cholesterol may slow coronary artery disease. Simvastatin is having a half-life of 2-3 hrs. The bioavailability of simvastatin tablets is approximately 5 %, with little inter subject variation. Due to these inherent draw backs of simvastatin, an alternative drug delivery system is needed to achieve maximum therapeutic efficacy and to improve patient compliance. Transdermal patch is one of the most feasible drug delivery system for such drugs [6, 7].

MATERIALS AND METHOD

Simvastatin was obtained as a gift sample from Themis Medicare Ltd, Mumbai. Hydroxypropyl Methylcellulose(HPMC)K4M was obtained as a gift sample from Colorcon Asia Pvt. Ltd. Polyvinyl Pyrolidone (PVP) K30, Dimethylsulphoxide(DMSO) and Propylene Glycol (PG) was obtained from Molychem .All other material were of analytical grade.

Compatibility Study

Compatibility Study Using FTIR[2, 8]

The compatibility study between pure drug and formulation was carried out using IR (Shimadzu IR Affinity 1). The compatibility study was carried out by using KBr pellet method. Drug-excipients mixture was subjected to different temperature and humidity conditions like 25^0C/60% RH for 1 month. KBr was dried in the oven at 40^0c and it was then mixed with the sample in a motor pestle. The sample was then compressed using a pellet press. The sample was placed in the IR sample holder. A background scan was taken followed by the IR scan of the sample.

Experimental Work

Formulation Development and Strategy

Screening of polymer and their combination[3, 4, 9]

Different polymers like Eudragit R-100, HPMC K4M, Ethyl cellulose, PVP using ratio of any two at a time were studied for their film forming property. Films were prepared using different ratio of above mentioned different polymer using solvent casting technique. The polymer film with various polymers in different concentrations was then checked for desired characteristics of film like physical appearance, tensile strength, folding endurance by a set of experiments. The polymer film prepared using Ethyl cellulose alone was found to be sticky and wet even after 24 hours. The polymer film prepared using 1% and 2% of Eudragit RL 100 and HPMC K4M using single polymer at a time were not possible to peel out from the mould without breaking the film. The polymer film form from PVP alone in different concentration was easily breakable while removing it from mould. The softness of polymer PVP film found to be increasing with increasing percentage of PVP used. Polymer films formulated using Eudragit RL 100, HPMC K4M and Ethyl cellulose in concentration of 3% were very thin and broken during handling. Polymer film prepared using HPMC K4M, Ethyl cellulose and Eudragit RL 100 in concentration 5% were thick and brittle. Finally the film formed using 4% of HPMC K4M, Ethyl cellulose and Eudragit RL 100 were selected for further studies for combination of two polymers , while PVP was used in 1% and 2% concentration as film formed was found to less breakable then film formed from higher concentration.

The various combination of polymer in 1:1 ratio is showed in table below.

Table 1: Composition of trial batches with polymers Eudragit RL 100, Ethyl cellulose, HPMC K4M and PVP K30 to select the polymer combination

Sr. No.	Polymer combination	Polymer ratio
1	Eudragit RL 100 : HPMCK4M	1:1
2	Eudragit RL 100 : PVP K30	1:1
3	Eudragit RL 100 : Ethyl cellulose	1:1
4	HPMC K4M : PVP K30	1:1
5	HPMC K4M : Ethyl cellulose	1:1
6	Ethyl cellulose : PVP K30	1:1

For above batches different evaluation was carried like weight, folding endurance, tensile strength and appearance. And from the evaluation performed it was found that film formed by polymer combination with 1:1 ratio of HPMC and PVP is more flexible and suitable for the formulation than other combination as film form by ethyl cellulose as one of polymer was breakable while handling as don't completely dry even after 48 hour resulting in very sticky film. The film formed using Eudragit as polymer were brittle and hard and were not easily removed from mould. Thus, polymer film consisting of HPMC and PVP as combination polymer forms flexible and strong film comparative to other polymer combinations. Further studies were carried out using different combination ratio of polymer HPMC: PVP.

Table 2: Polymer combination of HPMC and PVP in different ratio for selecting best polymer ratio

Sr. No.	Polymer combination	Polymer ratio
1	HPMC K4M: PVP K30	2:1
2	HPMC K4M: PVP K30	1:2
3	HPMC K4M: PVP K30	3:1
4	HPMC K4M: PVP K30	1:3

From the above polymer combination batches, the combination of HPMC K4M and PVP in the ratio 2:1 was found to give superior in appearance, tensile strength, folding endurance and weight over the other combination. Hence, remaining combination was not used for the further studies. Thus, further studies were carried out using this polymer combination of HPMC K4M: PVP at 2:1 concentration ratio along with the different penetration enhancer. The above various patch formed was tested for vario1sdesired characteristics like physical appearance, tensile strength, folding endurance by a set of experiments.

Selection of plasticizer[2,8]

For proposed formulation of polymer film, the plasticizers screened were propylene glycol, Oleic acid and glycerol. The optimum concentration of plasticizers was determined by formulating

transdermal patches with two different polymer ratio with plasticizer concentrations at 10%, 20%, 30% and 40%. Polymer film without drug using propylene glycol (PG) as plasticizer was found to exhibit ease of peeling and good appearance. The optimum concentration of plasticizer was determined by formulating the film with predetermined polymer concentration.

Selection of polymer combination[2, 12]

Batches with polymer combination of HPMC K4M: PVP K30 using DMSO and oleic acid as penetration enhancer

From above selection of polymer combination and plasticizer results, the following batches were made with combination of HPMC: PVP using DMSO (**Dimethylsulphoxide**), oleic acid and PEG 200 (**polyethylene glycol**) as the penetration enhancer. The batches were subjected to various evaluation parameters along with In-vitro diffusion study to determine the release rate of the formulation.

Table 3: Batches with polymer combination of HPMC K4M: PVP K30 using DMSO, PEG 200 and oleic acid as penetration enhancer[4]

Different Penetration Enhancer			
Ingredients	**DMSO**	**Oleic acid**	**PEG 200**
HPMC K4M(mg)	400	400	400
PVP K30(mg)	200	200	200
Simvastatin(mg)	30	30	30
DMSO	2ml	2ml	2ml
PG	10%	10%	10%
Methanol	2ml	2ml	2ml
Distilled water	10ml	10ml	10ml

As DMSO was found to give better penetration enhancement further studies were carried out using polymer film made using different concentration of DMSO as penetration enhancer. The polymers were selected and the batches were prepared using 2:1 ratio of the polymer combination using DMSO 3ml, 4ml and 5ml as penetration enhancer. The batches were evaluated for drug content uniformity along with the uniformity of the weight. All the batches were then subjected to diffusion study using Franz diffusion cell with cellophane membrane. The patch was cut into 1.5× 1.5 cm dimension for diffusion study. The diffusion cell was filled with the phosphate buffer pH 7.4 with stirring with help of magnetic stirrer for uniform mixing of medium. Patch was mounted on cellophane membrane. 1ml aliquot was withdrawn, suitable dilutions were made and sample was analyzed at 239nm using UV spectrophotometer.

Table 4: Batches with polymer combination of HPMC K4M: PVP K30 using DMSO in three different concentrations

Ingredients	D1	D2	D3
HPMC K4M(mg)	400	400	400
PVP K30(mg)	200	200	200
Simvastatin(mg)	30	30	30
DMSO	3ml	4ml	5ml
PG	10%	10%	10%
Methanol	2ml	2ml	2ml
Distilled water	10ml	10ml	10ml

D= DMSO

On the bases of the in-vitro diffusion study the most effective formulation was found to be D3.

Formulation of Medicated Transdermal patch[11, 12, 13

The transdermal patch of Simvastatin was prepared by simple solvent evaporation method. The polymers HPMC: PVP was dissolved in their respective solvents water and methanol respectively in optimized ratio and mixed together. Plasticizer was added to mixture of polymer and penetration enhancer was added drop wise to above mixture in pre-determined concentration. Simvastatin was dissolved in minimum amount of methanol separately. The solution of drug and above polymer mixture were mixed together with vigorous stirring. Prepared mixture was cast in rectangular glass mould and patch was allowed to dry. After complete evaporation of solvent the patch was removed and stored in aluminum foil in desiccators. The area of rectangular patch was calculated as:

Length of patch =6.5 cm, breath=4.5 cm

Area of patch = L×B= 6.5×4.5= 29.25cm^2

Dose Calculation[14]

The total dose of drug (Dt), in a prolonged action preparation comprises of the normal dose (Dn), and the sustaining dose (Ds) i.e. Dt= Dn+Ds

If the first order elimination rate constant is K

Then Dt = Dn(1+Kt) , Kt = t ^{½}

Where t ^{½} is biological half life

In case of Simvastatin the normal dose Dn is 10 mg and its biological half life Kt^{½} is 2 hours

Therefore, Dt= 10(1+2) = 30mg.

Experimental design[15]

Traditional methods of formulation by changing one variable at a time are very time consuming hence it become essential to use tools to minimize time and maximize utility. Hence the Software

Design Expert (version 9.0.2, Stat-Ease Inc, Minneapolis, MN) was used to optimize and evaluate main effects, interaction effects of formulation. A 2^2Design was used, the design contained two factors and two variables amount of polymer and concentration of penetration enhancer. The amount of drug was kept constant at 30 mg. Response chosen was physical appearance and drug release determined by *in vitro* diffusion study. Analysis of variance (ANOVA) and statistical analysis were also performed using the same software. The factors and their levels are depicted in Table. The Factorial design layout is represented in table 6

Table 5: Levels of polymer and penetration enhancer

Level of factor	Coded values	Amount of polymer (mg)	Amount of penetration enhancer(mg)
High	+1	200	5
Low	-1	100	3

Table 6: 2^2 Factorial design layout

Formulation code	Polymer	Penetration enhancer	Polymer (mg)	Penetration enhancer (ml)
P1	+1	+1	200	5
P2	+1	-1	200	3
P3	-1	-1	100	3
P4	-1	+1	100	5

Evaluation of Formulation[3, 16-19]

i) Physical appearance and Thickness

All the transdermal patches were visually inspected for colour, clarity, flexibility and smoothness. The thickness of each patch was measured at the different sites using screw gauge and the average thickness was calculated. Percentage deviation from mean thickness was determined.

ii) Weight variation

Five patches from each batch were weighed individually and the average weight was calculated.

iii) Drug content uniformity

Patches of specified area (1sq.cm) was cut into small pieces and dissolved in 10 ml of methanol and volume was made up to 50ml with phosphate buffer pH 7.4, further dilutions were given to 1ml stock solution upto 10ml with phosphate buffer pH 7.4.The solution was filtered and absorbance was taken at 239 nm. A blank was prepared using a drug-free patch (placebo) treated similarly.

iv) Folding endurance

The folding endurance was determined by repeatedly folding the patch at same place until it

shows any crack or break. The number of times the film could be folded without breaking/cracking gave the value of folding endurance.

v) Percent moisture loss

The prepared patches were weighed and kept in desiccators containing activated silica at 40^0C for 24 hours in a drier at least or more until it showed a constant weight. The percentage of moisture content was calculated by determining the difference between initial and final weight with respect to initial weight.

Percentage moisture loss= $(Initialweight - Finalweight)/(Initialweight) \times 100$

vi) Percent moisture uptake

The films were weighed accurately and placed in desiccators containing 100 ml of saturated solution of aluminium chloride (79.5% RH).After 3 days; the films were taken out and weighed. The percentage of moisture uptake was calculated as the difference between the final and initial weight with respect to the initial weight.

Percentage moisture uptake= (Final weight- Initial weight) /Initial weight) × 100

vii) Tensile strength

Film strip free from physical imperfections, was held between two clamps. The force and elongation was measured when the film broke. Measurements were run three times for each film. The tensile strength at break was calculated as below.

Tensile strength (Kg/mm^2) = Breaking force (Kg)/cross section area of sample (mm^2)

viii) *In-vitro* diffusion studies[10, 19]

Franz diffusion cell was used to perform diffusion study. A 1.5× 1.5 cm area of patch was cut and was used for diffusion study. The dialysis membrane was kept in between the donor and receptor compartments. The receptor compartment was filled with phosphate buffer pH 7.4 and maintained at 37^0C. Magnetic bar driven by a synchronous motor was placed in receptor compartment and driven at 100 rpm. At time intervals of 0.5,1,2,3,4,5,6 and 24 hr, 1ml of aliquot from receptor compartment was withdrawn, and the same volume of fresh medium was replaced into the compartment. The samples were analyzed spectrophotometrically for drug content at wavelength of 239 nm.

ix) Ex-vivo diffusion studies[20-25]

The ex-vivo skin permeation study was performed using Franz diffusion cell and prepared rat skin. The abdominal skin of male Wister albino rats (180 – 220 g) were used in this investigation. The hair was shaved off as close as possible to the skin without damaging it. After sacrificing the animal, a full thickness skin (i.e. epidermis with stratum corneum and dermis) was

excised from the shaved abdominal site. Any skin which had a disrupted barrier was rejected. After removing the fat and sub-dermal tissue, the skin was stored frozen at -20^{0}Cand used within one week. The skin was soaked in phosphate buffer overnight before the diffusion study. Skin was mounted between the two compartments. The dorsal surface of skin was placed in contact with the donor chamber. The receptor chamber was filled with PBS (pH 7.4) and stirred with a star-head Teflon magnetic bar driven by a synchronous motor. At time intervals of 0.5, 1, 2, 3, 4, 5, 6 and 24 hr. 1ml aliquot of receptor was withdrawn, and the same volume of fresh medium was replaced back into the chamber. The concentration of drug in the samples was analyzed spectrometrically by UV at 239nm and the percentage cumulative amount of drug release was plotted against time.

Mathematical Modeling of kinetic release[11, 16-19, 21-25]

In order to assess the kinetic release of the formulation, it was subjected to kinetic release models Zero and First order release model. R^2 values of both the orders were compared.

The mechanism of drug release of final formulation was determined by comparing slope values of Higuchi release model and Kormeyer-Peppas release model.

Scanning electron Microscopy (SEM) studies[12-19]

The surface morphology of the optimized patch was examined by scanning electron microscopy (ESEM Model Quanta) operated at 15 KV on samples, gold-sputtered for 120 seconds at 10 mA, under argon at low pressure. The study was conducted on dried optimized patch before and after the diffusion studies to observe the surface – topography of the patch.

Stability[26, 27]

The optimized patch was packed in aluminium foil and stored at room temperature in a desiccator containing saturated solution of sodium chloride (75% RH) and tested on 0th, 15th, 30th, 60th and 90th day. And the following parameters were evaluated

i) Physical appearance

ii) Folding endurance

iii)Drug content

iv)In vitro diffusion study

RESULT AND DISCUSSION

Formulation Development and Strategy

Preparation of transdermal patch without drug

The formulation of the patches was carried out using the solvent evaporation method using

distilled water as solvent for polymer and methanol as solvent for drug. The polymer patches were made in the fabricated glass moulds of dimension 6.5 × 4.5 cm. The results showed good compatibility of the polymers for the glass material. Thus further experiment was carried out using same glass moulds. In the study, four different polymers were studied for combination ratio for flexible patches with trial batch with different penetration enhancer to achieved maximum drug release from matrix to target. Also different percent of various plasticizers were used to get good transdermal patches.

Selection of polymer combination out of four polymers used HPMC K4M, PVP K30, Eugradit RL 100 and Ethyl cellulose

Table 7: Evaluation results for trial batches with polymers Eudragit RL 100, Ethyl cellulose, HPMC K4M and PVP to select the polymer combination

Sr. No	Polymer combination with 10% Plasticizer.	Polymer ratio	Appearance	Weight (mg)	Folding endurance	Tensile strength (Kg/cm^2)
1	Eudragit RL100 : HPMC K4M	1:1	Transparent	389±3	6	0.2±0.02
2	Eudragit RL100 : PVP K30	1:1	Transparent	294±2	8	0.1±0.02
3	Eudragit RL100 : Ethyl cellulose	1:1	Transparent	194±2	10	0.01±0.03
4	HPMCK4M : PVP K30	1:1	Transparent	338±2	93	0.36±0.03
5	HPMCK4M : Ethyl cellulose	1:1	Transparent	289±5	10	0.2±0.02
6	Ethyl cellulose : PVP K30	1:1	Transparent	409±3	Unable to fold	0± 0.01

The different patches prepared from different combinations of above four polymers in 1: 1 ratio showed a transparent, durable and flexible patch i.e. superior in physical property then other combinations for polymer combination HPMC: PVP. This combination showed transparent appearance along with high folding endurance of 93, weight of 338 mg and tensile strength 0.36 kg/cm^2 proving it strength to withstand long duration application and flexibility.

Table 8: Evaluation results for polymer combination of HPMC and PVP in different ratio for selecting best polymer ratio

Sr. No.	Polymer combination	Polymer ratio	Appearance	Weight (mg)	Folding endurance	Tensile strength (Kg/cm^2)
1	HPMCK4M : PVP K30	2:1	Transparent	343±0.2	73	0.347±0.41
2	HPMC K4M : PVP K30	1:2	Transparent	335±0.4	67	0.313±0.02
3	HPMC K4M : PVP K30	3:1	Transparent	409±0.2	56	0.364±0.03
4	HPMC K4M : PVP K30	1:3	Transparent	312±0.1	35	0.277±0.03

The studied carried out on trial batches of polymer combination HPMC: PVP in different combination ratio showed that the polymer ratio with ratio 3:1 forms hard patch difficult to remove from mould. The polymer ratio 1:3 formed a sticky and soft patch with is difficult to handle and easily breakable. The polymer ratio of 1:2 form wet soft breakable patch. Thus, the

polymer ratio of HPMC: PVP 2:1 formed patch which is more flexible, easy to handle and easy to remove it from mould, patch with good texture and tensile strength. Thus, futher studies were carried out using polymer combination of HPMC : PVP in ratio 2:1.

Selection of plasticizer

The plasticizer like propylene glycol, Oleic acid and glycerol with concentrations at 10%, 20%, 30% and 40% are used to find best plasticizer for patch preparation for easy of removing patch from mould and its flexibility. Th e propylene glycol was found to be best plasticizer giving desired quality to patch when PG being used in small concentration i.e. 10%.

Table 9: Peelable property of patch due to different concentration of three different plasticizer used

Plasticizer	Concentration			
	10%	20%	30%	40%
Propylene glycol	Easily peelable	Easily peelable	Not peelable	Not peelable
Oleic acid	Peelable with difficulty	Peelable	Sticky patch	Sticky patch
Glycerol	Peelable with difficulty	Peelable	Sticky patch	Sticky patch.

Selection of penetration enhancer

Table 10: *In-vitro* diffusion results for batches with polymer combination of HPMC K4M : PVP using DMSO and oleic acid as penetration enhancer

Sr. No.	Time (Hours)	%CPR(Cumulative percent drug release)		
		DMSO (2ml)	Oleic Acid (2ml)	PEG 200 (2ml)
1	0.5	0.692	0.546	0.514
2	1	0.887	0.603	0.549
3	2	1.213	0.672	0.592
4	3	1.543	0.956	0.643
5	4	1.960	1.008	0.698
6	5	2.346	1.345	0.874
7	24	63	51	45

The evaluation carried out for the patches prepared using polymer combination of HPMC K4M : PVP using DMSO, PEG 200 and oleic acid as penetration enhancer showed % cumulative release 63% of patch using DMSO as penetration enhancer to be higher then other two patches formed using Oleic acid and PEG 200 as penetration enhancer 51% and 45% respectively. Thus, DMSO showed greater penetration of drug through membrane in diffusion studies which is required for good drug penetration and release to target organ i.e. transdermal layer of skin.

Thus, further study was carried out to find best concentration of DMSO in patch to give maximum drug penetration and cumulative percent drug release in In-vitro diffusion study.

Table 11: Batches with polymer combination of HPMC K4M: PVP using DMSO in three different concentration

Sr. No.	Time (Hours)	%CPR(Cumulative percent drug release)		
		DMSO (3ml)	DMSO(4ml)	DMSO(5ml)
1	0.5	0.892	0.946	1.894
2	1	1.487	1.603	2.249
3	2	1.913	1.872	2.792
4	3	2.743	2.960	3.343
5	4	2.960	3.018	3.891
6	5	3.346	3.545	4.654
7	24	93	98	105

The *In-vitro* diffusion studied carried out for batches with selected polymer combination with different determined concentration of DMSO used as penetration enhancer showed the cumulative percent drug release greater for patch having DMSO in concentration of 5ml i.e. 105% which is high than the other two concentration of 3 ml and 4 ml. Thus, further batches were prepared using DMSO in concentration of 5ml as penetration enhancer.

Experimental Design

A 2^2 full factorial design was employed to study the effect of independent variable i.e. the amount of polymer and penetration enhancer on dependent variables i.e. percentage cumulative release and percent drug content. Amount of drug was kept constant at 30 mg. The diffusion study and drug content was performed and the results were fed into the software Design Expert. The data was analyzed by ANOVA and was reported to be significant. The selected independent variable significantly influenced the cumulative release and drug entrapment that is evident from the results in table 5. For cumulative release polynomial equation in terms of coded factors was obtained as

%cumulative release= +79.99 +18.49*A +13.51*B -5.49*AB

R^2 was found to be 0.9949 w of the which implies that 99.49% of the variation in the responses was attributed to independent variables. The Model F-value of 257.77 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. The signal to noise ratio of 37.79 implies that the model can be used to navigate the design space.

Table 12: R^2 valve for % cumulative release

Std.Dev	2.40	R-Squared	0.9949
Mean	79.99	Adj R-Squared	0.9910
C.V. %	2.99	Pred R-Squared	0.9794
PRESS	91.78	Adeq Precision	37.790

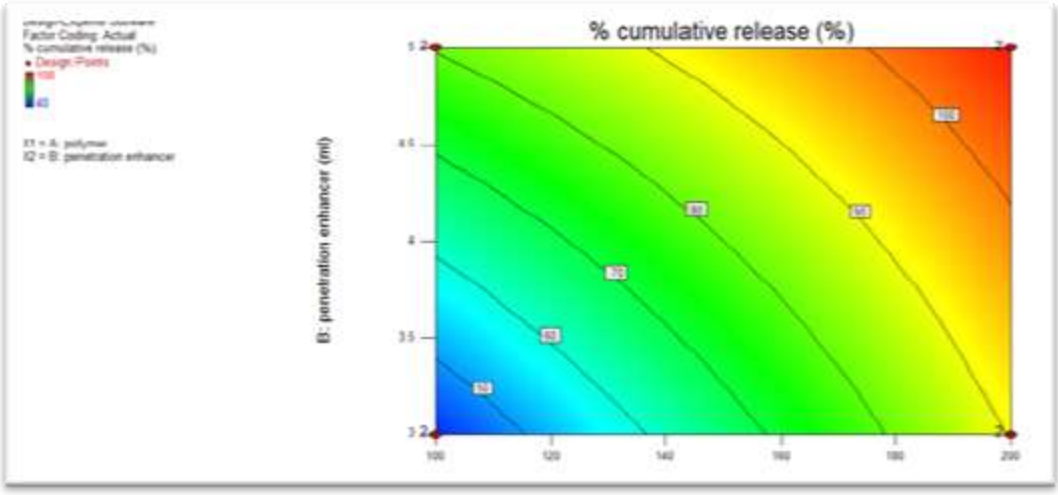

Figure 1: Contour plot for % cumulative release

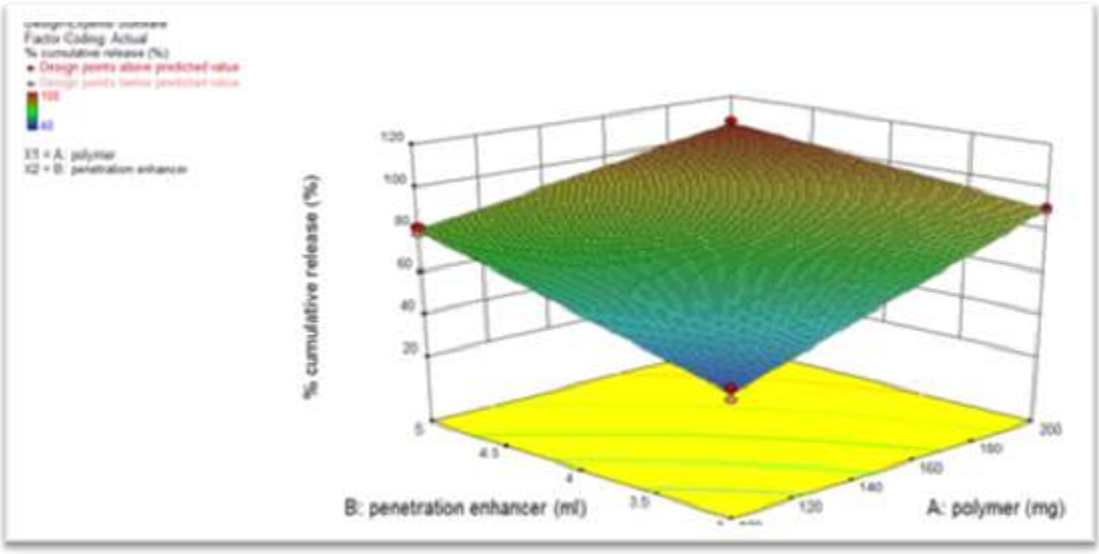

Figure 2: 3D surface plot for % cumulative release

In case of drug content the experimental data was fitted into a polynomial equation and equation in terms of coded factor for optimum drug content was found to be

Drug content = +97.36 +1.68*A +0.73*B +0.099*AB.

The $R^2$was 0.9962. "Adeq precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. The Model F-value of 219.00 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. The ratio of 33.639 indicate an adequate signal hence this model can be used to navigate the design space. Exhaustive grid survey showed that batch P1 was the optimized batch [50].

Table 13: R^2 valve for % drug content

Std.Dev	0.20	R-Squared	0.9939
Mean	97.36	Adj R-Squared	0.9894

C.V. %	0.21	Pred R-Squared	0.9758
PRESS	0.66	Adeq Precision	33.639

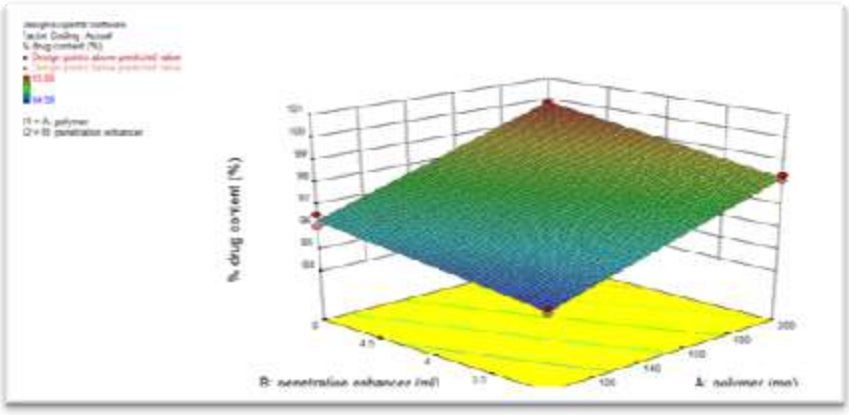

Figure 3: 3D surface plot for % drug content

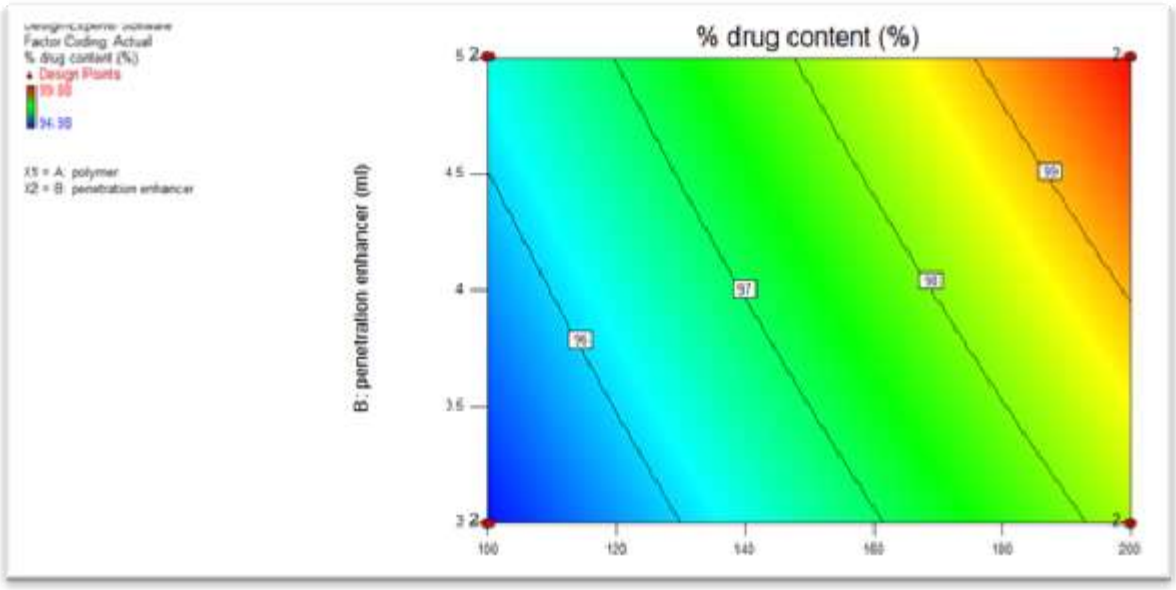

Figure 4: Contour plot for % drug content

Table 14: Responses for factorial design batches

Formula code	Polymer (mg)	Penetration Enhancer(ml)	% cumulative release	% drug content
P1	200	5	108	99.86
P2	200	3	89.69	98.33
P3	100	3	40	95.12
P4	100	5	79	96.56

Evaluation of Simvastatin Transdermal patch

i) Physical Parameters

a. Appearance:

The patches formed were transparent, smooth and uniform.

b. Thickness

Table 15: Evaluation of Simvastatin patch for mean thickness of patch

Formulation No.	Thickness(mm)					Mean Thickness (mm)	SD
P1	0.13	0.15	0.16	0.15	0.13	0.144	0.005477
P2	0.13	0.12	0.12	0.14	0.13	0.128	0.008367
P3	0.14	0.15	0.14	0.16	0.16	0.150	0.007071
P4	0.15	0.15	0.13	0.16	0.13	0.144	0.005477

Each value represents mean ± SD, n=5

Thus, thickness range of 0.12-0.16 for all patches of the batch and low standard deviation values in the film thickness measurements ensured uniformity of the patches prepared by solvent evaporation method.

ii) Weight Variation:

Table 16: Evaluation of weight variation for the individual formulations

Formulation	Weight variation(mg)					Mean (mg)	SD
P1	324	325	323	325	325	324.4	0.894427
P2	325	322	322	323	323	322.8	0.83666
P3	334	336	334	336	337	335.4	1.341641
P4	326	325	327	325	327	326	1

Each value represents mean ± SD, n=5

The weights ranged between 322-327 mg and with low standard deviation which indicates that different batches patch weights, were relatively similar.

iii) Drug content:

Drug content uniformity of the individual patch was evaluated using the stated method and absorbance was recorded in UV spectrophotometer at wavelength of 239 nm. The value was found to be satisfactory for P1 and P2 as the percent drug content was in the range 98-110% of the total drug incorporated.

Table 17: Drug content uniformity of Drug patches

Formulation No.	Drug content (%)
P1	99.86
P2	98.33
P3	95.12
P4	96.56

Thus, on bases of % drug content thee drug is found to be release in satisfactory range.

iv) Folding endurance

Folding endurance was measured by repeatedly folding the patches of predetermined sizes at a point until the crack was observed at that point. It was found that all the formulation had a

folding endurance greater than 300, results indicated that patches had optimium strength ensuring their integrity and applicability.

v) Percent Moisture loss :

The results are represented in Table. 18

vi) Percent moisture uptake:

The results are represented in Table. 18

vii) Tensile strength (Kg/sq.cm):

The results are represented in Table 18

Table 18: Results representing Percent Moisture loss, percent moisture uptake and tensile strength

Formulation No.	Percentage Moisture Loss(%)	Percentage Moisture Uptake(%)	Tensile Strength (Kg/sq.cm)
P1	9.8	3.5	0.57
P2	12	4.5	0.55
P3	10.2	4.9	0.51
P4	10.4	5.3	0.48

The percentage moisture loss for batch P1 9.8% was low in compared with other batches indicating small moisture loss for batch P1 thus, formulation of P1 helps the patch to remain stable, brittle and free from complete drying. The percentage moisture uptake for batch P1 3.5% was low in compared with other batches indicating low moisture absorption thus, formulation of P1 protects the material from microbial contamination and bulkiness of the patches. The patch of formulation P1 showed higher tensile strength than other patches thus, P1 showed higher strength.

viii) Diffusion study of Simvastatin patch

***In-vitro* diffusion studies**

Table 19: Percent cumulative release of transdermal patches using cellophane membrane

Time (Hour)	P1 (%)	P2 (%)	P3 (%)	P4 (%)
0.5	2.96	2.09	1.89	1.98
1	3.43	2.30	2.54	2.68
2	3.99	3.16	3.04	3.10
3	4.34	3.63	3.12	3.33
4	5.54	4.57	4.17	4.45
5	6.89	5.34	4.54	4.90
6	7.32	6.76	5.33	6.15
7	8.91	7.98	6.09	6.76
24	109.03	97.67	67.90	80.56

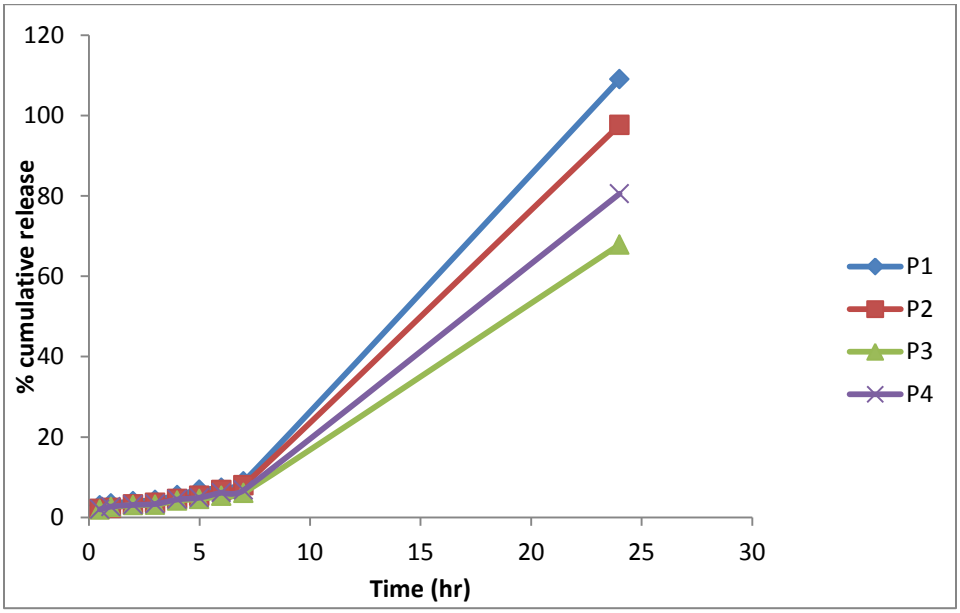

Figure 5: *In vitro* Drug release of batch P1-P4

The in-vitro diffusion studies from batch P1-P4 showed high cumulative % drug release for batch P1 compared to other batches having DMSO in concentration 5ml and HPMC:PVP ratio 2:1.

ix) *Ex-vivo* diffusion studies

Table 20: Percent cumulative release of transdermal patches using the abdominal rat skin. (879/ac/05/CPCSEA)

Time (hours)	% cumulative Release			
	P1	P2	P3	P4
0.5	2.6	2.3	0.78	0.85
1	3.5	2.8	1.23	1.32
2	4.17	3.8	2.56	2.67
3	4.6	4.6	3.12	2.95
4	4.9	5.0	3.45	3.95
5	5.5	5.8	4.2	4.67
6	5.98	6.07	4.56	5.18
7	6.7	6.34	5.67	5.95
24	108	89.6	40	79

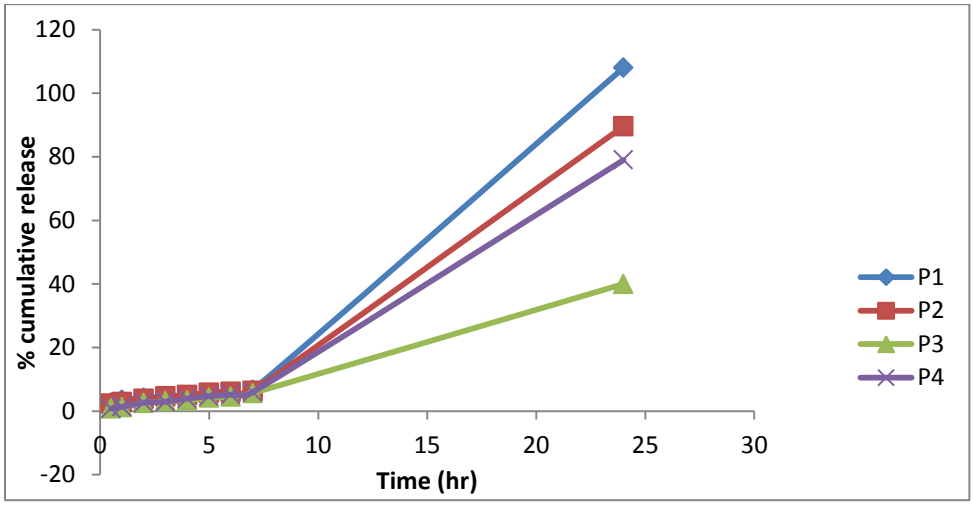

Figure 6: *Ex-vivo* drug release for batch P1-P4

The *ex-vivo* diffusion studies from batch P1-P4 showed high cumulative % drug release for batch P1 compared to other batches having DMSO in concentration 5ml and HPMC: PVP ratio 2:1.

Mathematical Modeling of Kinetic Release

The data analysis was carried out by fitting the data into different models and the results are given in table no.

Table 21: Regression Analysis of different models

Coefficient of correlation (R^2) values						
Zero order model		**First order model**	**Korsemeyer-Peppas Model**		**Higuchi model**	**Proposed mechanism of release**
0.96	75	0.8894	R^2 0.9885	N 0.48	0.9959	Higuchi model

According to the drug release kinetics the best linearity was found in Higuchi's equation plot with R^2 = 0.9959 indicating the release of drug from matrix as square root of time dependent process based on Fickian diffusion. Thus, the drug-release kinetics of transdermal patch of simvastatin in In-vitro release profiles of drug from formulation could be best expressed by Higuchi model of drug release. It depicts that drugs are release by diffusion. When the data were fitted into Korsmeyer - Peppas equation, the diffusion component (n) values ranging from 0<N<0.5 indicating that the Fickian diffusion was the predominant mechanism of drug release from the formulation [57]

Compatibility Study Using FTIR

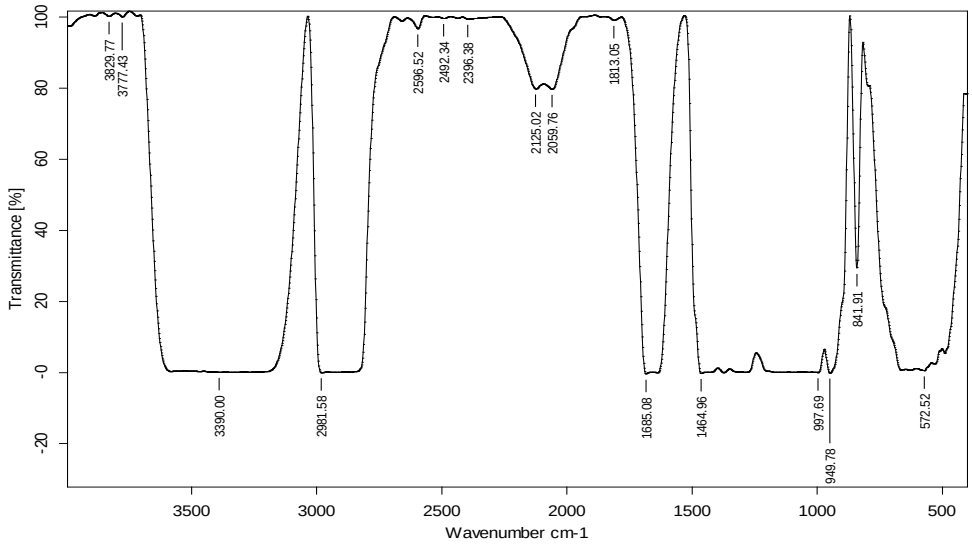

Figure 7: FTIR spectra of optimized batch

The FTIR study was carried out for the optimized patch and pure drug it was observed that there was no significant difference in characteristic peaks of pure drug and optimized patch revealing absence of any interaction.

SEM

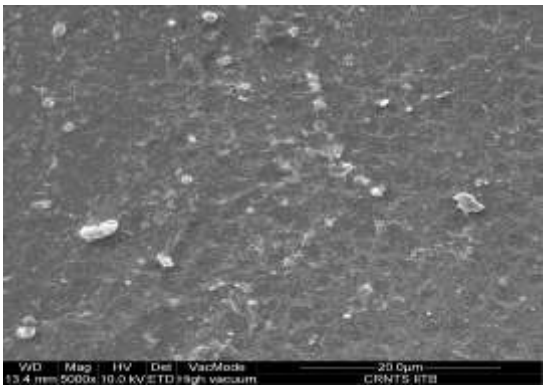

Figure 8: SEM of simvastatin optimized patch surface before diffusion

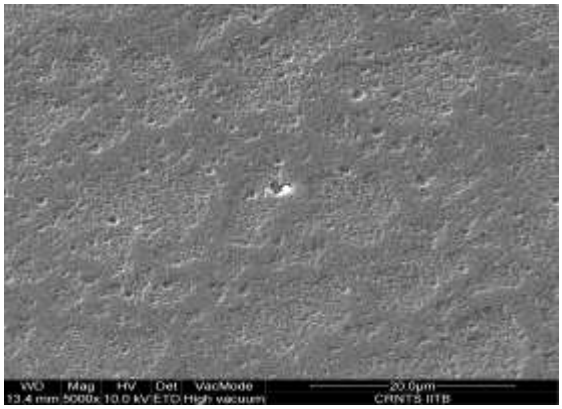

Figure 9: SEM of simvastatin optimized patch surface after diffusion

The model for carrying out SEM was ESEM QUANTA.

Figure 8.showed optimized patch before diffusion with intact surface with simvastatin drug particle dispersed in patch surface. The patch surface appears to be intact without any perforation or trough. Figure9. After diffusion for 24 hours the solvent enters the patch and drug diffuses out of the patch into the solvent i.e. diffusion medium. The image after diffusion showed a network in the swollen polymer through which the drug diffused to the diffusion medium. Thus, it was concluded that drug was released from patch by diffusion mechanism proposed by Higuchi model and shows that drug is release by diffusion.

5.10 Stability studies

1) Physical parameter, folding endurance, Drug content, In-vitro diffusion study.

Stability study was carried out for optimized batch P at 2-5 ^{0}C and 25 ^{0}C. The parameters on 0th, 15th, 30th , 60th ,90th day were as mentioned in Table No.

Table 22: Stability study of optimized Batch

Parameter	Condition	0th day	15th day	30th day	60th day	90th day
Appearance	2-5^{0}C/75%RH	+++	+++	+++	+++	+++
	25^{0}C /75%RH	+++	+++	+++	+++	+++
Thickness	2-5^{0}C/75%RH	0.147	0.147	0.147	0.147	0.147
	25^{0}C /75%RH	0.147	0.147	0.147	0.147	0.147
Folding endurance	2-5^{0}C/75%RH	>300	>300	>300	>300	>300
	25^{0}C /75%RH	>300	>300	>300	>300	>300
Drug Content	2-5^{0}C/75%RH	99.6	99.3	98.7	98.2	97.6
	25^{0}C /75%RH	99.6	99.1	98.5	98	97.1

Table 23: Percent cumulative drug release of simvastatin batch for stability study at 25^{0}C /75%RH

Time(hr)	Cumulative percent drug release (%)				
	0th day	15th day	30th day	60th day	90th day
0.5	2.7	2.6	2.4	1.9	1.5
1	3.4	3.3	3.2	2.5	2.1
2	3.9	3.8	3.7	2.7	2.5
3	4.3	4.4	4.2	3.2	2.9
4	4.8	4.7	4.6	3.9	3.2
5	5.6	5.5	5.4	4.5	3.6
24	101	99.56	97.98	94.34	91.55

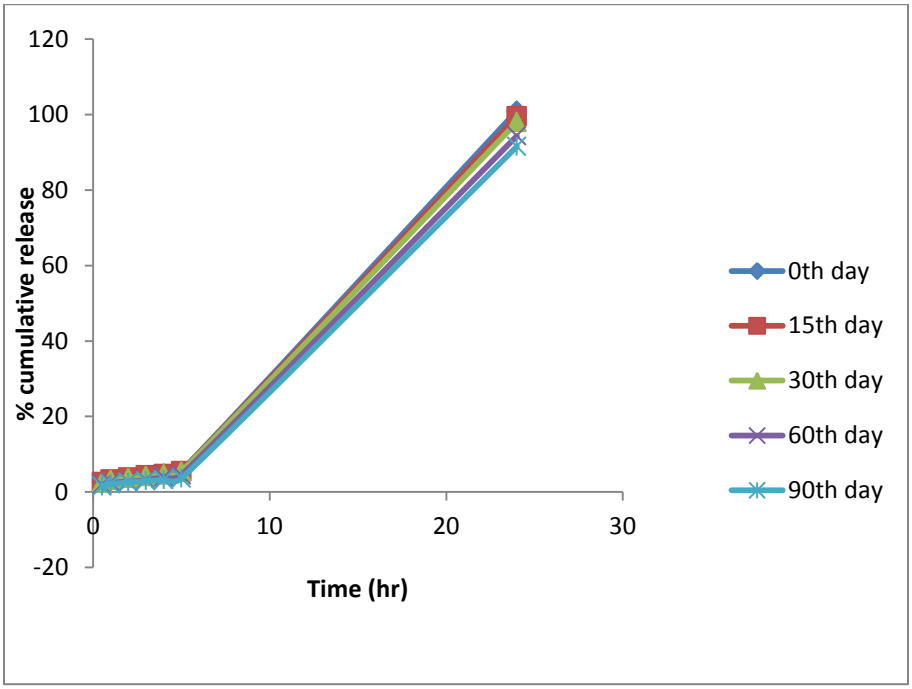

Figure 10: *In-vitro* drug release of simvastatin batch for stability study at 25^{0}C /75%RH

Table 24: Percent cumulative drug release of simvastatin batch for stability study at 2-5^{0}C /75%RH

Time(hr)	Cumulative percent drug release(%)				
	0th day	15th day	30th day	60th day	90th day
0.5	2.7	2.6	2.4	1.4	1.2
1	3.4	3.2	3.0	2.5	2.3
2	3.9	3.7	3.5	2.7	2.8
3	4.3	4.3	3.9	3.1	2.9
4	4.8	4.6	4.3	3.9	3.4
5	5.6	5.5	5.3	4.4	3.6
24	101	99.23	97	93.84	91.24

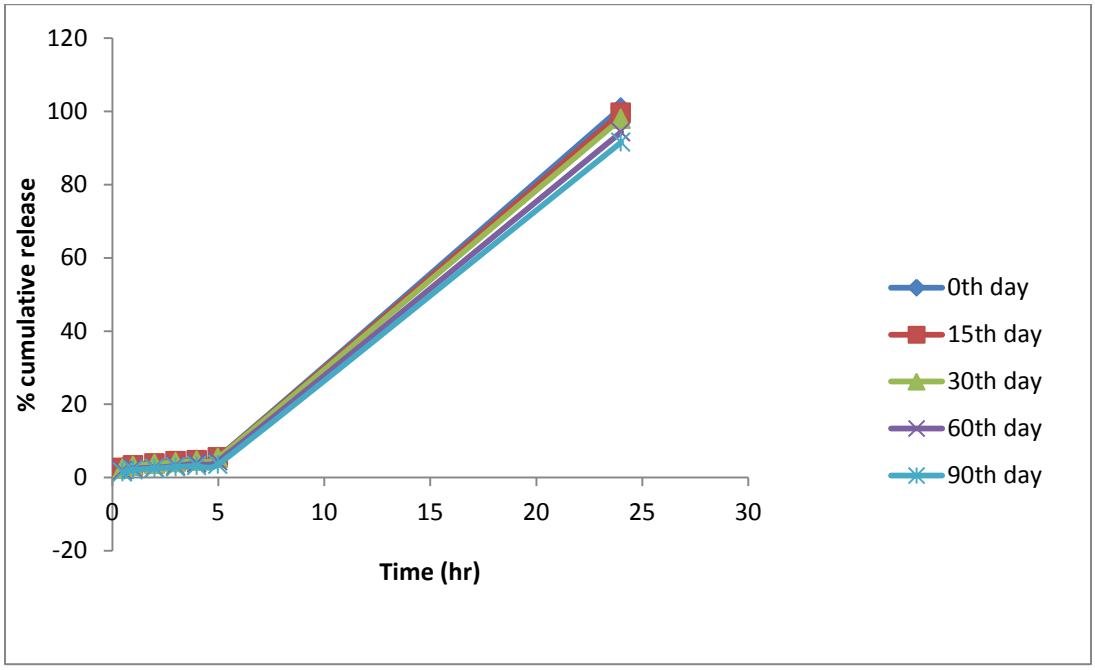

Figure 11: *In-vitro* drug release of simvastatin batch for stability study at 2-5^{0}C /75%RH

The stability study at 25^{0}C/75%RH and 2-5^{0}C/75%RH for three months showed stability for batch P1 with little deviation of cumulative drug release over stability study period.

CONCLUSION

It was found using exhaustive grid search that formulation P1 was the optimized formulation having % cumulative release 109 for in-vitro and 93.3 for *ex-vivo* and drug content 98.98%. The patch formulated was also uniform and had good physical characteristics. In- vitro and Ex-vivo diffusion study indicated sustained drug release over a period of 24 hours.

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