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Transdermal Delivery of Verapamil HCl: Effect of Penetration Agent on *In Vitro* Penetration through Rat Skin

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ABSTRACT

Verapamil Hydrochloride is a calcium channel blocking anti-anginal agent. Extensive first pass metabolism, low bioavailability (~20%) and short biological half life (4.8 hrs) altogether makes it an ideal candidate for transdermal drug delivery. The objectives of this study were to develop matrix-type transdermal patches of verapamil hydrochloride (VPL) with combinations of hydroxypropyl methyl cellulose (HPMC) and hydroxy propyl cellulose (HPC) as matrix polymers and to investigate the influence of oleic acid (OA) on *in vitro* permeation of VPL through rat skin. The permeation studies were performed using Franz-type diffusion cells and full-thickness excised abdominal rat skin. The effect of the polymers on the drug release, percentage moisture loss, percentage moisture absorption, folding endurance, and thickness, were investigated.. *In vitro* release studies showed zero-order release of the drug from all the patches, and the mechanism of release was diffusion mediated. Data was analysed using different release kinetic models. *In vitro* release profiles showed that from optimized combination the release of the drug was sustained and it extended over a period of 24 hr VPM 006 emerged as the most satisfactory formulation as far as its technological properties were concerned.

INTRODUCTION

Transdermal drug delivery is gaining importance due to its combined advantages over the oral and the transdermal route. It has the ability to improve the bioavailability, bypass hepatic clearance, enhance therapeutic efficacy and improve patience compliance (Allen et al., 2005; Barry, 2002; Cleary, 1984; Finnin et al., 1998). Transdermal delivery systems are classified in different categories, according to the technological basis of their approach, including the membrane permeation-controlled and the matrix diffusion-controlled transdermal therapeutic systems (Allen et al., 2005; Barry, 2002). Polymer matrices make good reservoirs for sustained release medications. There are many hydrophilic polymers used for transdermal drug delivery systems like polyvinyl alcohol (Ahmed et al., 2010; Barhate et al., 2011) and polyvinylpyrrolidone (Ahmed et al., 2010; Jayaprakash et al., 2010) and hydroxypropyl methylcellulose (Jayaprakash et al., 2010; Mehdizadeh et al., 2004), hydroxypropyl cellulose (Panchagnula et al., 2005; Funke et al., 2003). In the present study matrix type transdermal patches of HPMC and HPC has been prepared.

Drug permeation through the skin following transdermal delivery is also influenced by various design factors such as polymer species, internal structure of the polymer matrix and concentration of polymer matrix and drug (Hall et al., 2012; Kircik et al., 2010; Magnusson et al., 2001; Tiwari and Siahboomi, 2008; Vueba et al., 2006). Verapamil hydrochloride is a calcium channel blocker. On oral administration it undergoes extensive first pass metabolism which is responsible for its low bioavailability i.e. 20%. It has a short biological half life of just 4.8 hours, due to its short time of action it's required to be administered three times a day decreasing patient compliance. Due to its short $t_{1/2}$, high hepatic clearance, low bioavailability and low dose for administration verapamil hydrochloride can be considered as an ideal candidate for transdermal drug delivery (Batalis et al., 2007; Benet and Sheiner, 1980; MSDS Verapamil Hydrochloride). In the present investigation, the effects of polymer concentration, as well as their combinations on the *in vitro* release profile of verapamil hydrochloride from hydrated matrices of HPMC and HPC have been evaluated. HPMC and HPC are used as the release controlling polymers and oleic acid has been used as the penetration enhancer.

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MATERIALS AND METHODS

Materials

Verapamil hydrochloride B.P. was obtained as a gift from Abbott Piramal Ltd. Baddi. Hydroxypropyl Cellulose was obtained as a gift sample from Aurobindo Pharmaceuticals Hyderabad, India. HPMC was purchased from SD fine chemicals. All other chemicals such as Oleic acid, propylene glycol, Polyethylene glycol-400, Dichloro Methane (DCM) and methanol were of analytical grade.

Preformulation Studies

Dose calculation

The following parameters were ascertained before actual preparation of the patch. The required steady state plasma level concentration C_{SS} is 100 ng/ml (Benet et al., 1980; Devi et al., 2003). The required flux from the patch can be calculated from the following formula.

$$J = \frac{C_{ss} \times Cl_T \times BW}{A}$$

Where Cl_T is the rate of clearance of the drug from the body for a 70 Kg person = 11.85 ml/min/Kg, A is the area of the patch (25 cm^2) and BW is the Body weight of an average human (70 Kg). From the above calculations the flux was calculated as 200 $\mu g/cm^2/hr$ and the dose for a single patch for 24 hours was determined as Flux × Time × Area of Patch = 120 mg. It was decided that the drug would be present at 20% w/w concentration of the drug weight of the polymer so the dry weight of the polymer matrix would be 600 mg.

The penetration enhancer will be incorporated in the concentration of 20% w/w of the weight of the polymer and the plasticizer PEG-400 would be employed in the concentration range of 5% w/w of the dry weight of the polymer. The patch would further be surrounded by a parametric boundary of adhesive layer having a width of 1 cm^2.

Preparation of the adhesive Layer and casting materials

The adhesive layer was prepared using PVP K-30 and PEG-400 as described by Kanter; 2005. This was further optimized. A hollow square hollow cast was fabricated. The bottom of the mould was covered with the aluminium foil over which an aqueous solution of 4% polyvinyl alcohol was casted followed by drying in an oven at 60°C for 6 hours. The polymers were weighed in prerequisite amount and were dissolved in a mixture of isopropyl alcohol: deionized water (4:1)v/v. The solution was stirred to mix the components properly. After complete mixing the solution was casted over the PVA backing membrane. This layer was then evaluated for its adhesive properties.

Evaluation of different batches of adhesive layers

Thumb Tack Test

The thumb tack test was carried out by pressing the thumb lightly on the adhesive layer for 5 seconds and then withdrawing it. The difficulty with which the thumb was pulled back gave an idea about the adhesive strength, and comfort in its wear and removal. All the tests were performed in a blind way on 6 volunteers and the scoring was done in range of 0-5, with '0' indicating minimum adhesion and comfort and '5' indicating strong adhesion and comfort (Wongpayapkul et al., 2005).

Rolling Ball Test

In the rolling ball test (Pressure Sensitive Tape Council (PSTC) test no 6) a stainless steel ball of 11 mm diameter was rolled down an inclined plane having a length of 18 cm and inclined at an angle of 21° 30' to come into contact at the bottom with horizontal upward facing adhesive. The distance of the ball travelled out along the adhesive sample is taken as the measure of tack (Blake, 1975; Blake, 1983; Blake , 1986).

Creep Resistance / Shear Adhesion Test

The adhesive layer was cut into pieces 2.54 cm wide and 6 cm long. 1.27 cm of the specimen was applied at the tab end in contact with an adherent plate made of stainless steel. The specimen was laid without pressure exactly parallel to the length of the test surface and smoothed using a 2.04 Kg roller five times. The prepared sample was placed on the stand so that the panel make an angle of 2° inclined from the vertical so that the back of the panel formed an angle of 178° with the extended piece of sample. A weight of 500 g was secured to the free end of the patch. The test was performed with an apparatus made in our laboratory according to PSTC-1 specifications (Bottenberg et al., 1991; Mehdizadeh et al., 2004;Wongpayapkul et al., 2005).

Simplified peel adhesion test

The simplified peel adhesion 180° test is a combination of the creep resistance and peels 180° tests. Adhesive patches were cut into strips, 2.5 cm wide and 15 cm long, conditioned for 24 hours at 23±2°C and 50±5% RH. The samples, 6 cm of adhesive was applied to the adherent plate made of stainless steel, smoothed and peeled from the plate at 180° angle by a 500 gram mass. In this test, the peeling time is reported in minutes (Mehdizadeh et al., 2004)

Matrix preparation

A hollow square cast was fabricated. The bottom of the mould was covered with aluminium foil over which an aqueous solution of 4% polyvinyl alcohol was casted followed by drying in an oven at 60 °C for 6 hrs. The required amounts of polymers were dissolved in a mixture of DCM and methanol with constant stirring for proper mixing. The specified amount of drug, PEG-400, PG and oleic acid were added. The mixture was stirred for 2 hours to get a homogenous mixture. The solution was casted on PVA backing membrane and air dried. After complete drying, the layer was cut into pieces. These polymeric patches were cautiously placed in the centre of the adhesive side of the occlusive backing layer.

Characterization of prepared Transdermal Patches of Verapamil Hydrochloride

Physiochemical Evaluation

Thickness

The thickness of the patch was measured using micrometer screw gauge (Mitutoyo, Japan) from three different points. The average and the standard error mean (SEM) of the three readings was recorded (Mehdizadeh et al., 2004; Devi et al., 2003).

Drug Content Uniformity

The formulated film was taken and stirred with phosphate buffer pH 7.4 on mechanical shaker so as to allow the whole drug to dissolve. The solution was filtered and analysed spectrohotometrically at λ_{max} absorption maxima of 278 nm wavelength. The experiment was performed in triplicate and the results were reported as average ± SEM (Mehdizadeh et al., 2004; Devi et al., 2003).

Weight Variation Test

Three patches from each batch were weighed individually. The result of each batch was reported as average ± SEM (Mehdizadeh et al., 2004; Devi et al., 2003).

Tensile strength Test

The tensile strength was evaluated using in house fabricated instrument. A strip of 1 cm^2 was subjected to the test and the results were noted. The test was performed in triplicates and the result was reported in average ± SEM (Mehdizadeh et al., 2004; Devi et al., 2003).

Percentage Elongation

Percentage elongation was measured as difference in length of patch before and after it was subjected to tensile strength test. It was measured using a vernier calliper on addition of each weight until the strip broke. Percentage elongation is measured by the formula (Mehdizadeh et al., 2004; Devi et al., 2003).

$$\text{Percentage Elongation} = \frac{\text{Final Length} - \text{Initial Length}}{\text{Initial Length}} \times 100$$

Moisture Content Analysis

The patches were weighted individually and kept in desiccators at 37°C. The patches were weighted repeatedly at regular intervals until it attained constant weight. The final weight was noted when there was no further change in the weight of the individual patch. The percentage of the moisture content was calculated as a difference between the initial and final weight with respect to final weight (Naik et al., 1995).

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

The studies were carried out in triplicates for each batch. The average and SEM was determined.

Percentage Moisture Absorption

The patches were weighed accurately and placed in the environment of 75% RH. The patches were taken out periodically and weighed until no change in weight was observed. The percentage of moisture uptake was calculated as difference between final and initial weight of the patch with respect to the initial weight. The studies were carried out in triplicates for each batch (Naik et al., 1995)

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

Folding Endurance Test

For the folding endurance test the patch was folded from a same place repeatedly until the patch broke. In our case the breakage or disruption of the aluminium foil was considered as the point of breakage.

In vitro skin permeation studies

In vitro drug permeation studies were carried out using all glass modified Franz diffusion cell having an volume of 20 ml in the receptor compartment. Full thickness rat skin was utilized for the permeation studies.

Preparation of rat epidermis

Excised skin of wistar rats of either sex was used. Dorsal hair was removed with mechanical hair clippers followed by shaving the electric razor. The skin was wiped clean with physiological saline. The animal was sacrificed after 24 hours by spinal cord dislocation and dorsal skin was excised. The whole skin was soaked in water at 60°C for 45 seconds, followed by careful removal of dermis by gentle scraping, Freshly obtained epidermal skin was used in all experiments (Kingman et al., 2005).

Permeation Studies

Thermostatically controlled franz diffusion cell assembly was used for carrying out the permeation studies. Excised rat epidermis was placed over the receptor compartment with dermis facing towards donor compartment. Samples were withdrawn from the sampling port at predetermined intervals and the same quantity of fresh buffer was replaced at the same time to maintain sink conditions. Phosphate buffer pH 7.4 was filled in receptor compartment. The temperature was maintained at 32±2 °C and stirring rate was 100 rpm. The diffusion studies were carried out for 24 hrs. Samples were analyzed spectrophotometrically at absorption maxima of 278 nm.

Release Kinetics Study

Different kinetic models were used to analyse the mechanism of drug release from the transdermal patches. Zero order, First order, Higuchi matrix, and Korsmeyer Peppas models were applied to the release kinetics to explain the mechanism of release and the best fit model was selected by comparing the regression values obtained from different models.

Drug Polymer Interaction Studies

ATR-IR Studies Drug polymer interactions were evaluated using FTIR and ATR FTIR spectroscopy. ATR-FTIR spectra of the blank patches and the optimized formulation was carried out (FTIR ATR Thermo Scientific; NICOLET iS10) within the range of 4000 – 650 cm^{-1}.

Skin Irritation studies

Skin irritation studies were carried out using healthy albino rabbits weighing 1.2 to 1.5 Kg. The dorsal surface of the rabbit skin was cleared and the hair were removed by applying depilatory cream. The blank patches (without drug) of the optimized formulation were placed over the skin of the rabbit for 24 hours. After 24 hours, the skin was examined for any untoward reaction.

Stability Studies

Accelerated stability studies were conducted for the optimized patches according to ICH guidelines for 6 months. For stability study, the patches were taken, wrapped with aluminium foil and stored in the containers. The samples were withdrawn after 1, 2, 3 and 6 months and analysed for its drug content, tensile strength, elongation, weight variation, moisture content, moisture absorption and folding endurance.

Statistical Evaluation

The cumulative amount of drug release in 24 hours was tested for significant difference between different formulations using one way ANOVA with $P<0.5$ considered as statistically significant. Statistical analysis was done using Graph Pad Prism 5 and SPSS for windows software.

Table. 1: Composition of adhesive layer.

Adhesive	PVP K-30 (mg)	PEG -400 (mg)
Adv 1	50	75
Adv 2	100	75
Adv 3	150	75
Adv 4	50	100
Adv 5	100	100
Adv 6	150	100

RESULTS AND DISCUSSIONS

Evaluation of Adhesive Layer

The adhesive layer was evaluated by thumb tack test, rolling ball test, shear adhesion test & simplified peel adhesion test. In the thumb tack test the volunteers rated ADV 3 as the best combination on basis of adhesion and comfort, where as Adv 4 was found to be the least comfortable and had a slimy surface. Adv 3 also exhibited the maximum creep resistance time of 33.33 ± 1.45 min and the maximum peel adhesion time of 34.67 ± 0.88 sec proving its superiority as a better adhesive combination. However the same was not observed in the rolling ball test where Adv 3 covered the maximum distance of 18.30 ± 0.12 cm and the Adv 4 covered the least distance of 11.87 ± 0.18 cm this might be due to the fact that the adhesive requires small amount of pressure to restrain at the site of application. The results of the evaluation of the adhesive layer are summarized in Table: 3.

Evaluation of Transdermal Patch

Physiochemical Evaluation

Transdermal patches were evaluated for their physiochemical parameters such as thickness, drug content, weight variation, moisture content, percentage moisture absorption and tensile strength, percentage elongation and folding endurance. All the batches had satisfactory drug content and the folding endurance test depicted that the patches were robust enough to bear the daily wear and tear. The thickness of all the batches was found to range between 0.38 ± 0.01 to 0.43 ± 0.02 mm. The weight of the patch, % moisture content and % moisture absorption of the patch decreased with increasing concentration of HPC this may be attributed due to the fact that HPMC is more hydrophilic than HPC and therefore hydration rate is more (Hall and Read, 2012). The tensile strength and the percentage elongation was also seen to be dependent on the ratio of the polymers present. Increasing ratio of HPC also increased the tensile strength of the patch but on the same time decreased its elongation capacity as HPC exhibits stronger gel layer of the resultant matrix (Jiang and Zhou, 2003; Kingman et al., 2005). The results are summarized in Table: 4(a) and 4(b).

Table. 2: Composition of Verapamil Hydrochloride Patches.

Formulation Code	Verapamil (mg)	HPC (mg)	HPMC (mg)	OA (mg)	PG (mg)	PEG-400 (mg)
VPM 001	120	60	540	-	120	30
VPM 002	120	120	480	-	120	30
VPM 003	120	180	420	-	120	30
VPM 004	120	60	540	12	108	30
VPM 005	120	120	480	12	108	30
VPM 006	120	180	420	12	108	30
VPM 007	120	60	540	24	96	30
VPM 008	120	120	480	24	96	30
VPM 009	120	180	420	24	96	30

Table. 3: Results obtained from evaluation Parameters of Adhesive Layer.

Batch	Thumb Tack Test		Rolling Ball Test (cm)	Creep Resistance Test (min)	Simplified Peel Adhesion (sec)
	Adhesive Strength	Comfort			
Adv 1	2.00 ± 0.37	2.67 ± 0.21	15.16 ± 0.14	15.67 ± 0.88	9.67 ± 0.88
Adv 2	3.67 ± 0.21	2.75 ± 0.17	16.80 ± 0.11	28.00 ± 1.15	24.00 ± 2.31
Adv 3	4.08 ± 0.33	3.33 ± 0.42	18.30 ± 0.12	33.33 ± 1.45	34.67 ± 0.88
Adv 4	2.58 ± 0.42	1.50 ± 0.43	11.87 ± 0.18	14.00 ± 0.58	10.33 ± 1.45
Adv 5	3.17 ± 0.56	2.08 ± 0.54	13.30 ± 0.15	24.67 ± 0.33	23.33 ± 1.67
Adv 6	3.50 ± 0.43	2.33 ± 0.42	13.60 ± 0.06	28.33 ± 0.88	26.33 ± 1.20

Table. 4(a): Results obtained from physiochemical evaluation of transdermal patches.

Batch	Thickness	Drug Content	Weight Variation	Moisture Content
VPM 001	0.42 ± 0.03	99.08 ± 0.27%	1.715 ± 0.028	19.43 ± 1.19%
VPM 002	0.39 ± 0.01	99.73 ± 0.12%	1.683 ± 0.039	15.35 ± 1.81%
VPM 003	0.38 ± 0.01	99.81 ± 0.25%	1.622 ± 0.025	13.21 ± 1.21%
VPM 004	0.43 ± 0.02	99.67 ± 0.08%	1.713 ± 0.027	18.93 ± 1.16%
VPM 005	0.40 ± 0.03	99.40 ± 0.27%	1.659 ± 0.034	14.26 ± 1.60%
VPM 006	0.37 ± 0.01	99.19 ± 0.58%	1.589 ± 0.016	10.32 ± 0.83%
VPM 007	0.43 ± 0.01	99.50 ± 0.38%	1.694 ± 0.010	18.57 ± 0.44%
VPM 008	0.39 ± 0.09	99.14 ± 0.37%	1.637 ± 0.014	13.88 ± 0.66%
VPM 009	0.39 ± 0.04	99.22 ± 0.28%	1.566 ± 0.014	9.66 ± 0.73%

Table. 4(b): Results obtained from physiochemical evaluation of transdermal patches.

Batch	Moisture Absorption	Tensile Strength	Percentage elongation	Folding Endurance
VPM 001	10.58 ± 0.51%	739.67 ± 4.91	26.33 ± 2.60%	275 – 300
VPM 002	9.29 ± 0.21%	779.33 ± 10.84	20.00 ± 1.53%	275 – 300
VPM 003	6.49 ± 0.32%	819.33 ± 4.84	14.00 ± 1.53%	275 – 300
VPM 004	10.20 ± 0.26%	738.00 ± 4.04	26.00 ± 2.52%	250 – 275
VPM 005	9.01 ± 0.23%	778.00 ± 3.21	19.67 ± 1.76%	250 – 275
VPM 006	5.63 ± 0.29%	818.00 ± 3.46	13.67 ± 1.20%	250 – 275
VPM 007	9.75 ± 0.46%	738.33 ±1.76	26.67 ± 2.96%	250 – 275
VPM 008	7.17 ± 0.14%	778.33 ± 3.71	19.67 ± 1.67%	250 – 275
VPM 009	4.97 ± 0.12%	815.00 ± 6.08	13.67 ± 1.33%	250 – 275

Table. 5: Cumulative Percentage Drug Release from different batches.

T (hrs)	VPM 001	VPM 002	VPM 003	VPM 004	VPM 005	VPM 006	VPM 007	VPM 008	VPM 009
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	2.12±0.16	1.94±0.09	1.42±0.15	2.56±0.13	2.40±0.08	2.29±0.09	2.00±0.11	1.95±0.10	1.84±0.07
2	4.29±0.25	3.90±0.14	2.97±0.14	6.66±0.28	6.41±0.36	5.90±0.19	5.00±0.18	4.57±0.27	4.16±0.17
3	6.51±0.33	5.81±0.24	4.60±0.48	13.66±0.34	11.35±0.28	10.37±0.30	8.74±0.33	7.54±0.22	6.71±0.16
4	8.94±0.45	7.80±0.35	6.24±0.34	21.35±0.65	16.53±0.44	14.83±0.55	12.53±0.42	10.82±0.31	9.45±0.26
5	11.19±0.54	9.52±0.40	7.84±0.31	28.49±0.90	22.22±0.63	19.40±0.67	16.26±0.62	13.97±0.32	12.33±0.33
6	13.53±0.69	11.43±0.42	9.50±0.32	35.65±1.14	27±0.88	24.07±0.69	19.97±0.63	17.18±0.57	15.25±0.42
8	17.68±1.20	15.19±0.59	12.32±0.33	48.33±1.61	39.70±1.41	34.03±0.90	27.55±0.93	23.45±0.72	21.19±0.85
10	22.24±1.28	18.30±0.76	15.25±0.33	59.25±1.80	50.05±1.62	43.23±1.11	33.80±1.23	30.45±0.87	27.19±0.86
12	26.13±1.46	21.37±0.80	17.79±0.32	67.19±2.00	60.72±1.93	52.46±1.85	40.91±1.42	36.15±1.01	33.86±0.93
16	33.49±1.82	26.83±1.06	22.87±0.79	76.99±2.08	73.65±1.21	68.94±1.30	53.97±1.61	48.25±1.42	44.36±1.25
20	41.28±2.31	33.66±1.26	28.73±1.11	82.14±2.24	82.63±1.76	83.13±1.14	67.23±2.10	58.93±1.49	54.70±1.40
24	48.59±2.79	40.31±1.51	34.21±1.52	82.35±2.37	88.02±0.93	92.62±1.76	76.91±1.08	69.81±1.72	64.97±1.69

Table. 6: Release Kinetics Study of different formulations.

Batch	Zero Order	First Order	Higuchi	Korsmeyer Pappas Model	
	r^2	r^2	r^2	r^2	n
VPM 001	0.998	0.815	0.935	0.998	0.987
VPM 002	0.997	0.819	0.937	0.998	0.945
VPM 003	0.998	0.812	0.932	0.998	0.991
VPM 004	0.945	0.686	0.937	0.992	1.401
VPM 005	0.965	0.722	0.941	0.997	1.303
VPM 006	0.993	0.769	0.927	0.997	1.259
VPM 007	0.997	0.776	0.925	0.995	1.188
VPM 008	0.998	0.797	0.919	0.992	1.142
VPM 009	0.998	0.810	0.914	0.998	1.142

Table. 7: Stability studies of transdermal patches.

Time Months	Amount of Drug Remaining in mg (Percentage)	Tensile Strength (gm/cm^2)	Elongation (Percentage)	Weight Variation (gm)	Moisture Content (percentage)	Moisture Absorption (percentage)	Folding Endurance
0	119.16 ± 0.11 (99.30 ± 0.09%)	818.00 ± 3.46	13.67 ± 1.20 %	1.589 ± 0.016	10.32 ± 0.83	5.63 ± 0.29	250 - 275
1	117.17 ± 0.40 (97.64 ± 0.14%)	810.38 ± 4.39	13.71 ± 1.32 %	1.592 ± 0.032	10.38 ± 0.91	5.54 ± 0.38	250 - 275
2	115.50 ± 0.24 (96.25 ± 0.20%)	808.91± 4.81	13.94 ± 1.88 %	1.594 ± 0.029	10.41 ± 0.94	5.48 ± 0.34	250 - 275
3	114.63 ± 0.90 (95.53 ± 0.75%)	807.47 ± 6.31	14.10 ± 1.78%	1.601 ± 0.047	10.45 ± 0.92	5.47 ± 0.41	250 - 275
6	111.03 ± 0.98 (92.53 ± 0.82%)	804.42 ± 7.24	14.31 ± 2.2 %	1.604 ± 0.066	10.54 ± 0.85	5.34 ± 0.55	225 - 250

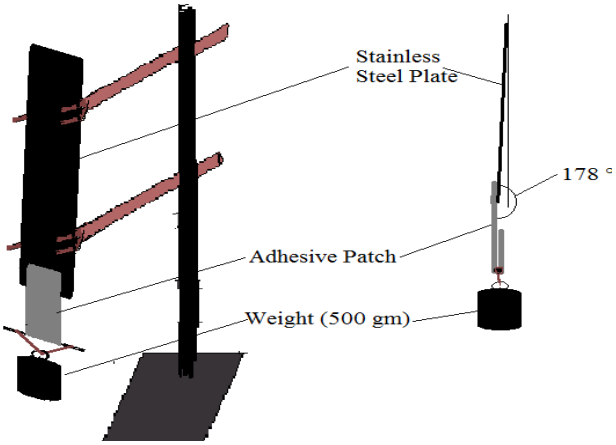

Fig. 1: Laboratory Apparatus for creep resistance test.

In vitro drug Permeation Studies

The rat skin was used to carry out the study. The results revealed that the flux was enhanced when 10% oleic acid was used as an additive with propylene glycol as penetration enhancers but increasing it up to the level of 20% decreased the flux across the skin. The increase in the flux might be due to the different mechanisms of penetration enhancement followed by propylene glycol and oleic acid as reported by other researchers. Oleic acid acts on the stratum corneum and disrupts its lipid structure by dual mechanism of lipid fluidization and lipid phase separation (Naik et al., 1995; Tanwar et al., 2007). On the other hand propylene glycol has a normal solvation and humectant for decreasing the barrier effect of the stratum corneum and does not alter the structure of stratum corneum (Kirchik et al., 2010; Magnusson et al., 2001). The decrease in the flux was observed when oleic acid was added beyond 10% w/w in propylene glycol might be due to the saturation effect of oleic acid over stratum corneum 20% w/w in propylene glycol. The formulation VPM 004 achieved the highest flux but its release was limited up to 20 hours and it depicted lower release profile of 82.35% cumulative release. The formulation VPM 006 showed drug release for up to 24 hours at an appreciable flux ranging around 200 µgm/cm^2/hr. The flux was decreased as the concentration of HPC was increased in the patch. The release profiles of VPM 004, VPM 005 and VPM 006. It was also observed that the rate of flux tended to decrease after the patch released 70% of the total formulation. The release data for all the patches is given in Table 5 and the graphical representation of percentage drug release versus time is given in Figure 2.

The graph depicting the change in rate of flux over time is given in Figure 3. It was also observed that only formulation VPM 004, VPM 005, VPM 006 were able to deliver the drug at a release rate of more than 200 µg/cm^2/hr. Though VPM 004 exhibited a highest flux of 344.03 ± 14.5 µg/cm^2/hr but its steady state flux dropped to 117 ± 0.99 µg/cm^2/hr and drug release was observed up to 20 hours. Formulation VPM 005 was able to release the drug above the required release rate of 200 µg/cm^2/hr for 12 hours but later its release rate was dropped to 107.32 ± 10.54 µg/cm^2/hr, although the release was observed for 24 hours but its release was quite less than the required rate. The formulation VPM 006 released the drug at values either above or close to 200 µg/cm^2/hr for 20 hours after which its release rate was dropped to certain extent. However it is important to note that no lag time was observed in any of the cases.

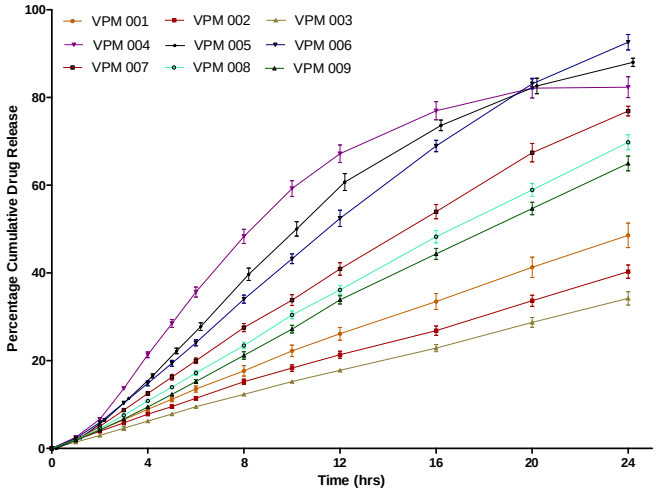

Fig. 2: *In-vitro* release profile of different formulations

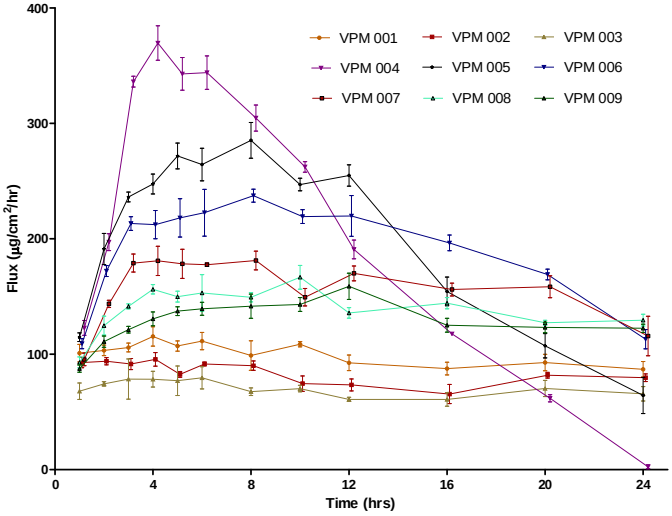

Fig. 3: Release Rate (Flux) of the different formulations.

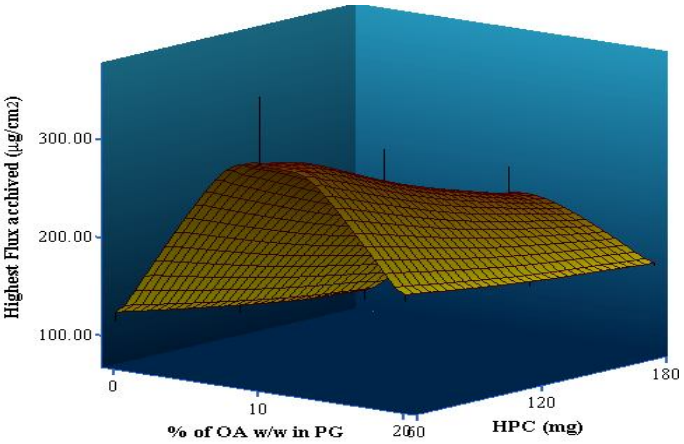

Fig. 4: Surface Response plot representing the highest flux achieved using different formulation variables

The release data was treated statistically using one way ANOVA and the release profiles of all the formulations were different from each other ($P<0.05$). The surface response curve elucidated the highest flux achieved by different formulations using different combination of HPC and penetration enhancer combination is given in Figure 4.

Release Kinetics Study

The release profiles were fitted in the various kinetic models. The coefficient of determination (r^2) was found to be much closer to 1 for Korsmeyer-Peppas equation. The mechanism of release was determined by n value of Korsmeyer Peppas model. VPM 001, VPM 002 and VPM 003 follow non fickian diffusion with n values ($0.5<n<1.0$) of 0.987, 0.945 and 0.991 respectively. The rest of the formulations follow Super case II transport as their n values were greater than 1.0 Table 6. This means that the formulation is following more than one type of release profiles possibly owing to chain disentanglement and swelling of hydrophilic polymers (Dey et al., 2010; Tanwar et al., 2007). The effect can be attributed to swelling exponent furthermore the mechanism of action of oleic acid on lipid fluidization and lipid extraction is one of the major contributions in enhancement of flux.

Drug Polymer Interaction Studies

The ATR FTIR spectrum of the blank patch and the optimized patch (VPM 006) is given in Figure 5. Characteristic peaks of Verapamil were observed at 1260 (C-O stretching in aromatic ring), 1591, 1514 and 1461 (C=C in aromatic ring), 1019 (C-N aliphatic stretching), 816 and 764 (meta substituted benzene) confirming the presence of verapamil in the patch. The ATR FTIR of the blank patch showed peaks at 3600-3000 (-OH asymmetric stretching band) and 1075-1175 (-C-O asymmetric stretching band). The peak at 1597 is related to the presence of hydrogen bonding between the HPMC and HPC molecules. This study shows that there was no interaction between the excipients and API of the formulated patch.

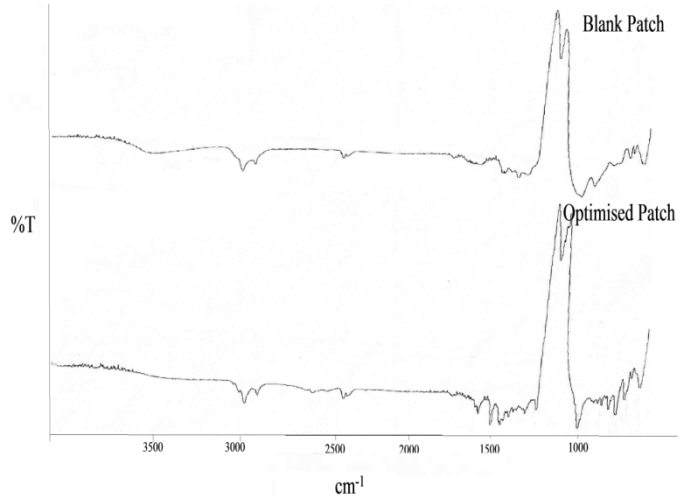

Fig. 5: ATR-FTIR of blank patch and the drug loaded patch.

Skin Irritation Studies

The skin was evaluated for signs of erythema or edema before the application and after the removal of the patch. There were very mild signs of erythema but no signs of edema were observed after 24 hours of application of patch. Figure 7 and 8 depicts the image of rabbit skin before and after the application of patch respectively. The patch can be considered non irritating to the skin and hence safe.

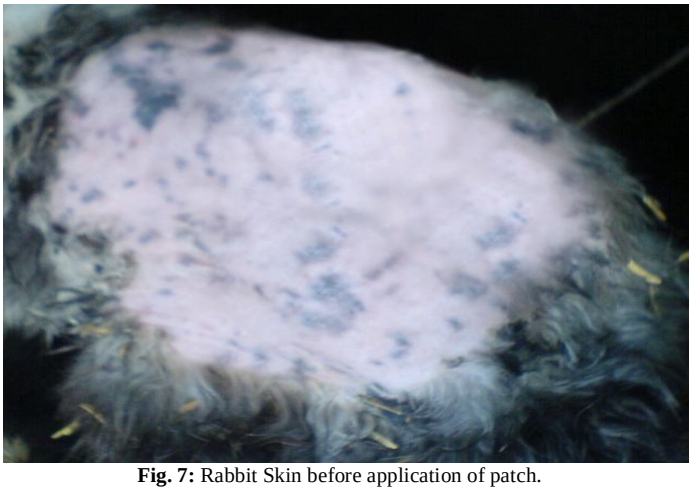

Fig. 7: Rabbit Skin before application of patch.

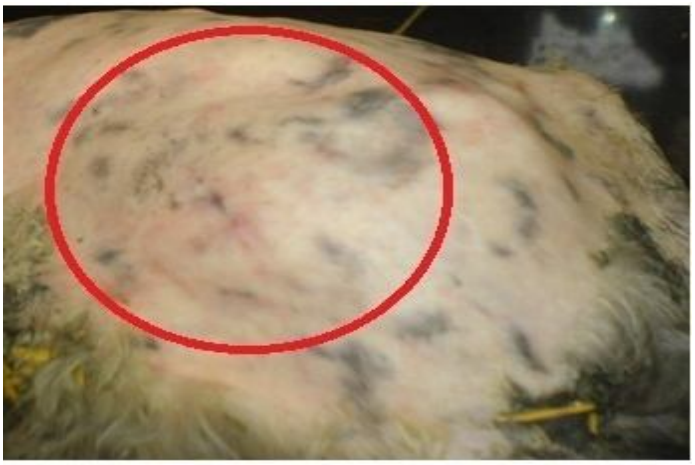

Fig. 8: Rabbit Skin after the removal of patch after 24 hours. (The marked region shows the slight signs of erythema at the site of application).

Stability Studies

Stability studies of the optimized formulation VPM 006 were carried out by storing formulation accelerated stability conditions (i.e. 40 ± 0.5 °C and 75 ± 0.5% RH) for 6 month. The samples were withdrawn after 1, 2, 3 and 6 months. The results of stability studies are given in Table 7 and the percentage of drug degraded with the function of time is depicted graphically in Figure 6. The formulation showed good stability for the entire time period of stability testing. No significant variation was observed on the rest of the physiological parameters. Over the entire time period the tensile strength, percentage moisture absorption and folding endurance decreased marginally whereas the percentage elongation and moisture content increased slightly.

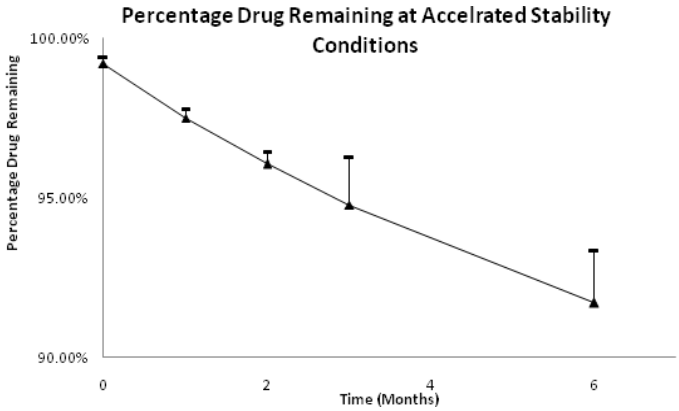

Fig. 6: Percentage of drug remaining in the transdermal patch after storage and accelerated stability conditions.

CONCLUSIONS

Transdermal patches of Verapamil Hydrochloride were prepared using HPC and HPMC as the sustain release polymers and using Oleic acid and Propylene glycol as the penetration enhancer. The incorporation of oleic acid helped to enhance the penetration by detanglement of the lipid layer and the increase in the concentration of HPC helped in maintaining the rate of release at a constant level. Hence, a sustain release polymeric transdermal patch of verapamil hydrochloride was prepared which was able to deliver the drug at constant rate through the dermal barrier.

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