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Development and Evaluation of Flupirtine Maleate Transdermal Patch Containing Different Permeation Enhancers

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ABSTRACT

The present study was aimed at the formulation of transdermal patches of flupirtine maleate containing different permeation enhancers. It acts indirectly as N-methyl-D-aspartate (NMDA) receptor antagonist and activates the K^+ channels; thereby acts as a skeletal muscle relaxant. Flupirtine maleate transdermal patches are intended to provide localized effect. The patches were prepared by solvent evaporation technique, using polyvinyl alcohol (PVA) as the polymer whereas dimethyl sulfoxide (DMSO) and polyethylene glycol (PEG-400) as the permeation enhancers. Methanol was used as a solvent to dissolve the drug and glycerol was used as the plasticizer. These patches were evaluated for *in vitro* permeation, tensile strength, percent moisture absorption, drug content uniformity, film thickness, weight variation and folding endurance. All the patches showed extended release properties. Formulation FDD8 containing 8% polymer and 2% DMSO was found to be the optimized formulation on the basis of evaluation parameters. *In vitro* permeation release was found to be 95.71 ± 0.01% at the end of 12 h. As the concentration of DMSO increased, the release profile of drug was enhanced. This indicated that DMSO improved the release profile of flupirtine maleate when compared to PEG-400. The release kinetics of the transdermal patches followed Higuchi matrix model. The stability studies showed that all the optimized patches were stable during their study period. From the present study, it can be concluded that addition of DMSO yields good result to enhance the permeation of the drug.

Keywords: flupirtine maleate, transdermal patch, permeation enhancers, dimethyl sulfoxide DMSO, polyethylene glycol PEG-400, polyvinyl alcohol PVA.

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INTRODUCTION

For many decades, treatment of an acute or chronic pain has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, creams, pills, suppositories, ointments, liquids, aerosols, injectable, etc. Analgesics for systemic action are preferably and routinely administered by the conventional oral dosage forms. Due to increased dose frequency, the patient compliance decreases. Therefore drug administration through transdermal route can be used as patient-friendly and compliant dosage form.[1] Transdermal patches are defined as medicated adhesive patch that are placed on skin to deliver a specific dose of medication through the skin and into the blood stream.[2] Flupirtine maleate is an NMDA receptor antagonist which blocks K^+ ions and blocks the pain pathway. It is an excellent alternative to opioids and NSAIDs. Therefore it has been chosen to be incorporated into transdermal patches for localized effect and it also helps to reduce the dosing frequency in patients.[3]

MATERIALS AND METHOD

Flupirtine maleate was procured as a gift sample from Lupin pharmaceuticals, Mumbai. Polyvinyl alcohol was procured from Central drug house limited, New Delhi. Polyethylene glycol 400 and glycerol were procured from Loba chemie, Mumbai. Dimethyl sulfoxide was procured from Himedia laboratories, Mumbai and methanol was procured from SRK chemicals, Mangalore.

Formulation of PVA patches containing drug and permeation enhancers: Solvent evaporation method.[4]

Required amount of PVA was weighed and dissolved in distilled water using magnetic stirrer and left undisturbed overnight to de-aerate. The drug was dissolved in methanol and the drug solution was added to the polymeric solution in small portions with constant stirring using a magnetic stirrer. Glycerol was added to the solution and different concentration of permeation enhancers were added to the respective formulations. The solutions were poured into petridish and placed in vacuum oven at 35°C overnight. The dried patches were cut into 1.5 X 1.5 cm using sharp blade and stored.

Table 1: Formulation of flupirtine maleate transdermal patches

Code	Drug (mg)	PVA (mg)	DMSO (ml)	PEG 400 (ml)	Glycerol (ml)	Methanol (ml)	Distilled Water q.s.(ml)
FD1	3115	600	-	-	0.5	15	25
FD2	3115	800	-	-	0.5	15	25
FDD1	3115	600	0.5	-	0.5	15	25
FDD2	3115	600	1.0	-	0.5	15	25
FDD3	3115	600	1.5	-	0.5	15	25
FDD4	3115	600	2.0	-	0.5	15	25

FDD5	3115	800	0.5	-	0.5	15	25
FDD6	3115	800	1.0	-	0.5	15	25
FDD7	3115	800	1.5	-	0.5	15	25
FDD8	3115	800	2.0	-	0.5	15	25
FDP1	3115	600	-	0.5	0.5	15	25
FDP2	3115	600	-	1.0	0.5	15	25
FDP3	3115	600	-	1.5	0.5	15	25
FDP4	3115	600	-	2.0	0.5	15	25
FDP5	3115	800	-	0.5	0.5	15	25
FDP6	3115	800	-	1.0	0.5	15	25
FDP7	3115	800	-	1.5	0.5	15	25
FDP8	3115	800	-	2.0	0.5	15	25

Physical appearance[5]

All the transdermal patches were visually inspected for color, flexibility, homogeneity and smoothness.

Percentage moisture absorption[6]

Each formulation was accurately weighed and exposed to ambient atmospheric conditions of temperature and RH for three days. After three days, the films were again weighed and percentage moisture absorption was calculated. Average percentage moisture absorption of each film was calculated.

Film thickness

The thickness of the patches were measured at five different places on a single patch of each formulation using a micrometer screw gauge and the mean values were calculated.

Weight variation

A set of three patches were weighed to calculate the weight variation.

Folding endurance[7]

A strip of 1.5 cm × 1.5 cm (2.25cm^2) was subjected to folding endurance by folding the patch at the same place repeatedly several times until a visible crack was observed and the values were reported.

Tensile strength and percentage elongation

The strips were pulled at a rate of 100 mm/min; the force and elongation were measured when the film broke. The pressure gauge directly gives readings in Kg/cm^2. Six trials were conducted for each patch.

Drug content uniformity[8]

A patch of size 2.25 cm^2 containing 100 mg of flupirtine was shredded and transferred into a graduated flask containing 10 ml DMSO. The flask was shaken for 24 h in a mechanical shaker.

Then the solution was filtered and after suitable dilutions with phosphate buffer pH 7.4, the absorbance was measured at 250 nm using the placebo patch solution as blank and the drug content was calculated.

***In vitro* drug release**

It was carried out using USP-II dissolution apparatus. 900 ml of PBS at 37 ± 0.5 ºC was taken as dissolution media. The rpm of the paddle was fixed at 100. Aliquot of 10 ml was withdrawn at an interval of 1 hour up to 12 h and absorbance was recorded at 250 nm.

***In vitro* drug permeation[9]**

The *in vitro* drug permeation was studied using a modified Franz diffusion cell. The donor compartment was in contact with ambient conditions of the atmosphere. The receptor compartment was in contact with 25 ml phosphate buffer pH 7.4 and the contents were stirred at 50 rpm at 37 ± 0.5 ºC for 12 h. Patch of 2.25 cm^2 containing 100 mg of flupirtine was placed in the donor compartment of the diffusion cell. The receptor fluid (2 ml) was withdrawn at predetermined time intervals. The samples were analyzed for drug content at 250 nm using UV-Visible spectrophotometer after suitable dilutions using the placebo patch solution as blank.

Stability study

Stability study was carried out as per ICH Guidelines at 25±2ºC/60±5% RH and 40±2ºC/75±5% RH for the optimized formulations of transdermal patches for appearance, percentage drug content, tensile strength and drug release.

***In Vivo* Skin Irritation Studies in Albino Wistar Rat[10]**

For skin irritation studies 8 albino rats of either sex were used. The rats were anesthetized using anesthetic ether and 3 cm^2 area was shaved on the either sides of the rats. Three optimized patches i.e. one containing drug alone, one containing drug along with DMSO as permeation enhancer, one containing drug with PEG 400 as permeation enhancer were used. A placebo patch containing only the polymer and excipients were also used to test the primary skin irritation. These patches were cut into a size of 2.25 cm^2 surface area and each was applied on the rats, right side serving as test and left as control (without drug) and was secured using adhesive tape. The patches were applied for 24 h and then observed for period of 72 h for any sign of erythema or edema and graded according to the standards.[10]

RESULTS AND DISCUSSION

In the present study, an attempt was made to formulate flupirtine maleate transdermal patch. Formulations were subjected to various parameters such as moisture absorption, film thickness, weight variation, folding endurance, tensile strength, percentage elongation, drug content

uniformity, *in vitro* drug release, *in vitro* drug permeation and *in vivo* skin irritation studies. All the patches prepared with different concentration of polymer were found to be flexible, smooth, translucent, non-sticky and homogeneous. This may be due to the presence of plasticizer.

Stability studies were performed as per ICH-Guidelines. Figure 1 and Figure 2 show the FT-IR spectra of pure drug and excipient which showed that there is no interaction found between drug and excipient. All the formulations showed good physical appearance as shown in Figure 3. The weight variation was found to be in range of 7.29 – 8.99g. Film thickness was found to be in the range of 0.32 – 0.44 mm. Folding endurance was found in the range of 200 - 300 folds, indicated that all the patches have good flexibility due to adequate quantity of plasticizer. Percentage drug content was found in the range of 91.77 – 95.95%. The results of weight variation, film thickness, folding endurance and drug content uniformity are depicted in Table 3.

Percentage moisture absorption was found to be in the range of 2.32 ± 0.02% to 3.35 ± 0.08%; whereas tensile strength was found to be in the range of 1.88 – 2.38 Kg/cm^2 and percentage elongation was found to be in the range of 30.45 - 38.62%. The results of percentage moisture absorption, tensile strength and percentage elongation are depicted in Table 4.

The in vitro dissolution study of formulation FD2 without permeation enhancer was found to be 69.95±0.11%, FDD7 with DMSO as permeation enhancer was found to be 99.73±0.02% as shown in Figure 4 and FDP8 with PEG-400 as permeation enhancer was found to be 99.89±0.05% as depicted in Figure 5. The details of *in vitro* dissolution studies are shown in Table 5 and Table 6.

In vitro drug permeation using Franz diffusion cell for formulation FD2 was found to be 69.95±0.11%, FDD7 was found to be 99.73±0.02% and FDP8 was found to be 83.45±0.05%. The details of *in vitro* drug permeation study are shown in Table 7 and depicted graphically in Figure 6.

In vivo skin irritation studies were carried out on 8 albino rats of each sex. The results show that the excipients incorporated in the patch do not cause any irritation to the rats. The extent of skin irritation was found to be below 1. The details of skin irritation study is given is Table 10 and depicted in Figure 7.

Table 2: Interpretation of FTIR spectrum

Group	**Wave numbers cm^{-1}**		
	Flupirtine maleate	**PVA**	**Physical mixture**
OH bond	-	3642.34	3774.06
CH_2 bond	-	1873.97	1702.12
C-O stretch	1277.81	1118.95	1224.07
C-H stretch (aliphatic)	-	2671.70	2313.96
C-H stretch (aromatic)	3046.75	-	2889.13
NH bend (primary amine)	1625.15	-	1702.12
NH_2 stretch	3256.35	-	3187.80

C-N stretch	3740.44	-	3774.43
C=C stretch (ring)	1500	-	1566.06

Table 3: Physicochemical properties of the prepared transdermal patches

Formulation Code	*Weight (g) ± SD	*Thickness (mm) ± SD	Folding Endurance	*% Drug Content ± SD
FD1	7.29 ± 0.11	0.32 ± 0.01	>250	92.21 ± 0.01
FD2	8.99 ± 0.08	0.41 ± 0.08	>250	95.19 ± 0.04
FDD1	8.97 ± 0.01	0.33 ± 0.02	>250	94.32 ± 0.08
FDD2	8.93 ± 0.06	0.39 ± 0.06	>250	93.26 ± 0.05
FDD3	8.29 ± 0.09	0.32 ± 0.03	>250	94.98 ± 0.01
FDD4	8.61 ± 0.11	0.37 ± 0.07	>250	95.02 ± 0.03
FDD5	8.33 ± 0.02	0.42 ± 0.04	>250	94.80 ± 0.04
FDD6	8.42 ± 0.13	0.43 ± 0.11	>250	93.87 ± 0.09
FDD7	8.01 ± 0.07	0.41 ± 0.10	>250	92.11 ± 0.02
FDD8	8.13 ± 0.04	0.42 ± 0.05	>250	93.24 ± 0.07
FDP1	7.97 ± 0.08	0.31 ± 0.03	>250	95.95 ± 0.03
FDP2	7.89 ± 0.13	0.34 ± 0.07	>250	94.74 ± 0.08
FDP3	8.34 ± 0.11	0.32 ± 0.04	>250	95.08 ± 0.02
FDP4	8.05 ± 0.02	0.30 ± 0.05	>250	95.23 ± 0.01
FDP5	7.62 ± 0.09	0.41 ± 0.12	>250	94.46 ± 0.05
FDP6	8.11 ± 0.01	0.44 ± 0.09	>250	95.59 ± 0.04
FDP7	7.96 ± 0.07	0.40 ± 0.03	>250	91.77 ± 0.07
FDP8	8.09 ± 0.06	0.41 ± 0.07	>250	93.02 ± 0.03

Table 4: Percentage moisture absorption, percentage elongation and tensile strength of the prepared transdermal patches

Formulation Code	*Percent Moisture Absorption ± SD	*Tensile strength (kg/cm^2) ± SD	*Percent Elongation ± SD
FD1	2.32 ± 0.02	1.88 ± 0.05	31.86 ± 0.47
FD2	2.99 ± 0.01	2.14 ± 0.03	33.72 ± 0.35
FDD1	2.91 ± 0.03	1.98 ± 0.11	30.45 ± 0.53
FDD2	2.86 ± 0.06	2.12 ± 0.13	31.63 ± 0.58
FDD3	2.97 ± 0.01	1.99 ± 0.09	32.84 ± 0.41
FDD4	3.02 ± 0.09	1.89 ± 0.10	34.06 ± 0.39
FDD5	3.13 ± 0.04	2.23 ± 0.08	32.37 ± 0.32
FDD6	3.10 ± 0.11	1.99 ± 0.04	35.97 ± 0.36
FDD7	3.35 ± 0.08	2.28 ± 0.07	36.02 ± 0.45
FDD8	3.28 ± 0.05	2.37 ± 0.10	38.62 ± 0.40
FDP1	2.76 ± 0.03	1.98 ± 0.04	31.19 ± 0.27
FDP2	2.69 ± 0.09	1.91 ±0.08	35.03 ± 0.38
FDP3	2.38 ± 0.02	2.03 ± 0.03	32.94 ± 0.35
FDP4	3.10 ± 0.13	1.76 ± 0.07	31.83 ± 0.26
FDP5	3.17 ± 0.07	2.29 ± 0.10	32.08 ± 0.22
FDP6	3.23 ± 0.01	2.32 ± 0.11	34.67 ± 0.38
FDP7	3.29 ± 0.11	2.37 ± 0.13	34.99 ± 0.41
FDP8	3.24 ± 0.03	2.38 ± 0.02	35.23 ± 0.53

Table 5: *In vitro* percentage cumulative drug release profile of transdermal patches containing DMSO

Time (h)	*%Cumulative drug release ± SD							
	FDD1	FDD2	FDD3	FDD4	FDD5	FDD6	FDD7	FDD8
1	12.25 ± 0.19	14.14 ± 0.06	18.99 ± 0.03	19.49 ± 0.02	8.97 ± 0.03	9.79 ± 0.02	10.51 ± 0.03	13.18 ± 0.02
2	21.54 ± 0.06	28.35 ± 0.11	29.68 ± 0.01	32.25 ± 0.11	16.28 ± 0.09	18.15 ± 0.09	22.46 ± 0.09	25.93 ± 0.01
3	32.96 ± 0.15	40.19 ± 0.02	43.15 ± 0.08	46.72 ± 0.07	25.11 ± 0.01	27.32 ± 0.07	34.35 ± 0.02	37.27 ± 0.09
4	40.49 ± 0.18	56.65 ± 0.07	60.44 ± 0.09	62.14 ± 0.04	36.54 ± 0.07	39.41 ± 0.08	44.99 ± 0.01	47.82 ± 0.05
5	65.34 ± 0.23	77.99 ± 0.05	79.39 ± 0.05	81.36 ± 0.06	42.19 ± 0.04	47.23 ± 0.03	49.11 ± 0.07	51.93 ± 0.07
6	74.25 ± 0.04	90.24 ± 0.09	98.56 ± 0.04	98.99 ± 0.01	50.43 ± 0.05	53.67 ± 0.01	58.52 ± 0.04	65.33 ± 0.03
7	87.99 ± 0.18	99.21± 0.13	---	---	58.16 ± 0.02	62.35 ± 0.05	67.21± 0.09	81.86 ± 0.01
8	99.48 ± 0.02	---	---	---	64.27 ± 0.09	70.14 ± 0.04	78.96± 0.03	84.52 ± 0.08
9	---	---	---	---	71.36 ± 0.11	79.39 ± 0.09	85.29± 0.08	89.79 ± 0.02
10	---	---	---	---	77.47 ± 0.08	85.57 ± 0.02	92.64 ± 0.01	95.63 ± 0.05
11	---	---	---	---	80.18 ± 0.10	91.42 ± 0.01	95.15± 0.04	98.72 ± 0.07
12	---	---	---	---	89.44 ± 0.05	95.83 ± 0.08	99.73 ± 0.02	---
13	---	---	---	---	94.17 ± 0.07	99.46 ± 0.05	---	---
14	---	---	---	---	99.32 ± 0.12	---	---	---

Table 6: *In vitro* percentage cumulative drug release profile of transdermal patches containing PEG 400

Time (h)	*% Cumulative drug release ± SD							
	FDP1	FDP2	FDP3	FDP4	FDP5	FDP6	FDP7	FDP8
1	10.82 ± 0.01	12.13 ± 0.02	15.96 ± 0.01	17.87 ± 0.10	6.31 ± 0.11	8.99 ± 0.01	9.68 ± 0.01	10.54 ± 0.03
2	21.43 ± 0.18	24.16 ± 0.01	29.19 ± 0.03	31.63 ± 0.05	11.11 ± 0.02	13.59 ± 0.07	19.36 ± 0.07	21.68 ± 0.04
3	37.11 ± 0.03	38.76 ± 0.10	40.18 ± 0.07	43.38 ± 0.02	16.63 ± 0.07	19.89 ± 0.03	24.03 ± 0.04	28.87 ±0.09
4	46.38 ± 0.21	49.88 ± 0.04	50.39 ± 0.10	52.72 ± 0.09	22.17 ± 0.03	26.23 ± 0.02	30.36 ± 0.09	34.15 ± 0.07
5	58.96 ± 0.17	61.11 ± 0.07	62.38 ± 0.09	64.95 ± 0.05	28.29 ± 0.08	31.38 ± 0.05	37.15 ± 0.01	42.98 ± 0.08
6	72.69 ± 0.26	75.46 ± 0.03	69.15 ± 0.08	76.39 ± 0.02	34.01 ± 0.10	38.17 ± 0.06	41.36 ± 0.02	49.69 ± 0.01
7	79.35 ± 0.11	80.21 ± 0.05	77.34 ± 0.11	89.13 ± 0.04	39.64 ± 0.09	44.79 ± 0.03	49.21 ± 0.08	56.66 ± 0.02
8	85.93 ± 0.16	86.42 ± 0.11	88.23 ± 0.01	98.65 ± 0.07	44.11 ± 0.11	47.13 ± 0.09	54.16 ± 0.02	60.32 ± 0.06
9	90.13 ± 0.08	91.59 ± 0.08	99.03 ± 0.04	---	49.36 ± 0.01	52.18 ± 0.08	63.11 ± 0.05	67.73 ± 0.01
10	98.36± 0.10	99.47 ± 0.10	---	---	54.18 ± 0.02	58.99 ± 0.05	69.93 ± 0.10	72.89 ± 0.09
11	---	---	---	---	60.34 ± 0.05	65.67 ± 0.07	76.11 ± 0.11	79.68 ± 0.10
12	---	---	---	---	69.73 ± 0.03	72.59 ± 0.01	80.03 ± 0.03	83.45 ± 0.05
13	---	---	---	---	74.98 ± 0.05	79.09 ± 0.03	86.93 ± 0.03	92.97 ± 0.05

14	---	---	---	---	80.49 ± 0.10	84.53 ± 0.06	92.54 ± 0.05	99.89 ± 0.05
15	---	---	---	---	88.53 ± 0.03	90.83 ± 0.02	99.06 ± 0.02	---
16	---	---	---	---	92.37 ± 0.07	99.93 ± 0.06	---	---
17	---	---	---	---	98.38 ± 0.03	---	---	---

Table 7: Comparative *in vitro* percentage cumulative drug permeation profile of optimized transdermal patches FD2, FDD7 and FDP8

Time (h)	*% Cumulative drug permeation ± SD		
	FD2	FDD7	FDP8
0	0	0	0
1	5.95 ± 0.10	10.51 ± 0.03	10.54 ± 0.03
2	10.37 ± 0.18	22.46 ± 0.09	21.68 ± 0.04
3	20.63 ± 0.07	34.34 ± 0.02	28.87 ±0.09
4	27.89 ± 0.02	43.97 ± 0.01	34.15 ± 0.07
5	34.41 ± 0.17	49.14 ± 0.07	41.91 ± 0.08
6	37.69 ± 0.13	57.55 ± 0.04	49.64 ± 0.01
7	45.26 ± 0.26	65.20 ± 0.09	55.67 ± 0.02
8	48.94 ± 0.19	76.94 ± 0.03	60.32 ± 0.06
9	53.38 ± 0.05	87.26 ± 0.08	67.73 ± 0.01
10	58.89 ± 0.16	93.64 ± 0.01	82.89 ± 0.09
11	61.16 ± 0.13	96.13 ± 0.04	99.68 ± 0.10
12	69.95 ± 0.11	99.73 ± 0.02	83.45 ± 0.05

Table 8: Stability studies of Transdermal patches at 25±2 ºC (Relative humidity 60 ± 5 %)

Formulation Code	Study duration (days)	Test parameters			
		Appearance	*% Drug content ± SD	*Tensile strength (kg/cm^2)± SD	*Drug release (12th h)± SD
FD2	30	Smooth and flexible	86.97 ± 0.11	2.13 ± 0.01	68.93 ± 0.02
	60	Smooth and flexible	86.94 ± 013	2.11 ± 0.06	67.91 ± 0.12
	90	Smooth and flexible	86.96 ± 0.22	2.14 ± 0.02	68.69 ± 0.13
FDD7	30	Smooth and flexible	86.92 ± 0.12	2.96 ± 0.02	98.86 ± 0.03
	60	Smooth and flexible	86.89 ± 0.04	2.95 ± 0.04	99.63 ± 0.12
	90	Smooth and flexible	86.91 ± 0.01	2.99 ± 0.18	99.67 ± 0.06
FDP8	30	Smooth and flexible	88.41 ± 0.10	2.96 ± 0.03	82.10 ± 0.17
	60	Smooth and flexible	88.38 ± 0.13	2.99 ± 0.01	83.07 ± 0.12
	90	Smooth and flexible	88.39 ± 0.12	2.97 ± 0.09	82.91 ± 0.11

Table 9: Stability studies of transdermal patch at 40±2 ºC (Relative humidity 75 ± 5 %)

Formulation Code	Study duration (days)	Test parameters Appearance	*% Drug content ± SD	*Tensile strength (kg/cm^2)± SD	*Drug release (12th h)± SD
FD2	30	Smooth and flexible	86.93 ± 0.04	2.12 ± 0.01	67.91 ± 0.01
	60	Smooth and flexible	86.98 ± 0.01	2.14 ± 0.13	66.90 ± 0.01
	90	Smooth and flexible	86.97 ± 0.1	2.10 ± 0.07	67.93 ± 0.05
FDD7	30	Smooth and flexible	86.93 ± 0.05	2.95 ± 0.11	98.61 ± 0.01
	60	Smooth and flexible	86.90 ± 0.06	2.92 ± 0.03	98.66 ± 0.07
	90	Smooth and flexible	86.93 ± 0.04	2.96 ± 0.05	99.63 ± 0.02
FDP8	30	Smooth and flexible	88.43 ± 0.01	2.93 ± 0.07	82.09 ± 0.08
	60	Smooth and flexible	88.37 ± 0.07	2.96 ± 0.11	83.06 ± 0.06
	90	Smooth and flexible	88.40 ± 0.06	2.95 ± 0.06	82.14 ± 0.04

Table 10: Readings after skin irritation study

Formulation Code		Erythema and Scar formation time (hours)				Oedema formation				Primary Irritation Index
	Rat Number	0	24	48	72	0	24	48	72	
F3	Rat 1	0	0	0	0	0	0	0	0	0
	Rat 2	0	0	0	0	0	0	0	0	0
FD2	Rat 3	0	0	0	0	0	0	0	0	0
	Rat 4	0	0	0	1	0	0	0	0	0.12
FDD7	Rat 5	0	0	0	0	0	0	0	0	0
	Rat 6	0	0	0	1	0	0	0	0	0.12
FDP8	Rat 7	0	0	0	0	0	0	0	0	0
	Rat 8	0	0	0	0	0	0	0	0	0

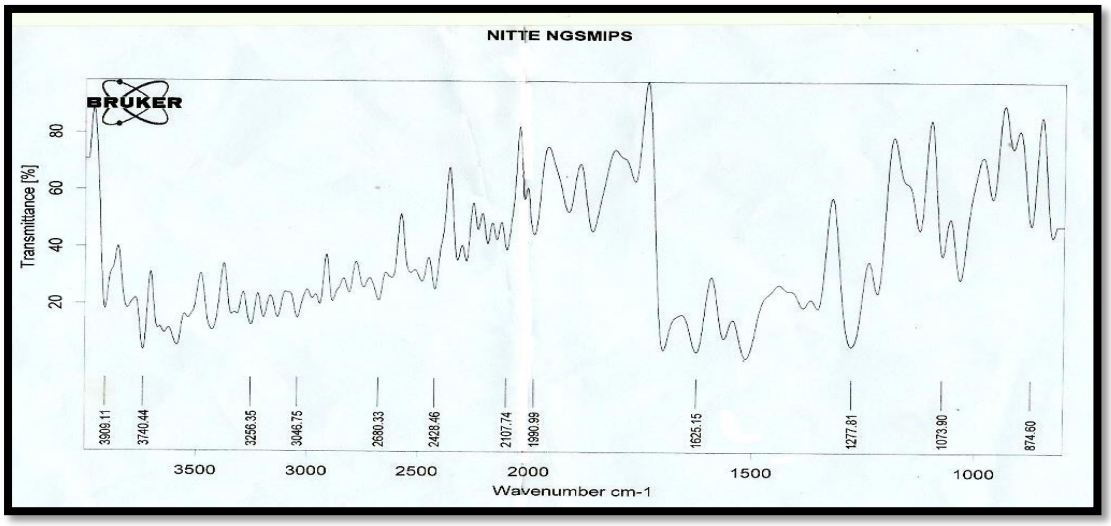


Figure 1: FTIR spectra of flupirtine maleate

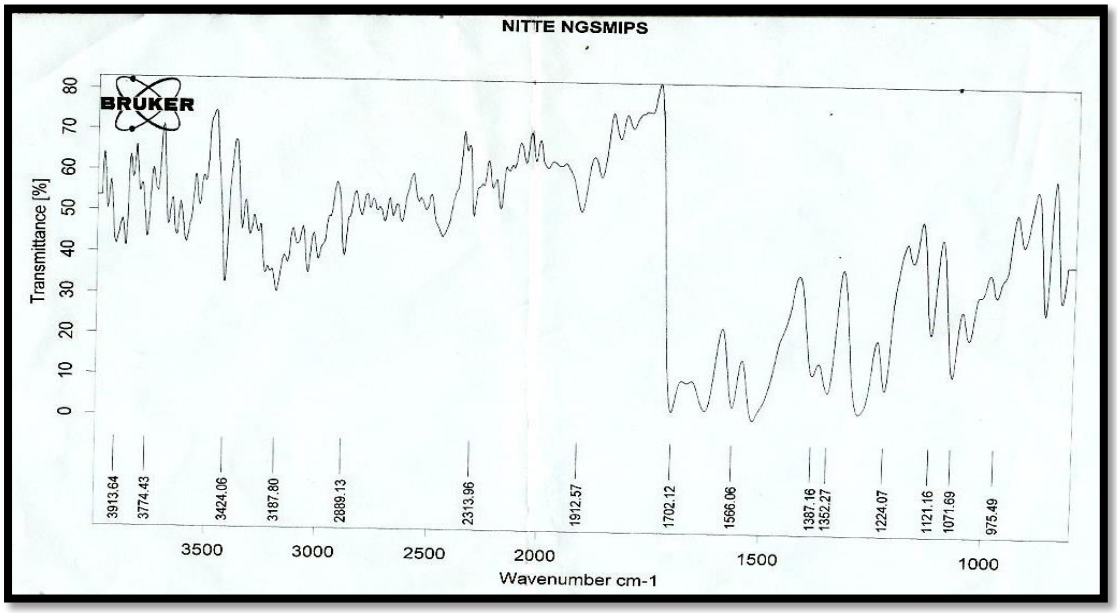


Figure 2: FTIR spectra of physical mixture of flupirtine maleate and PVA

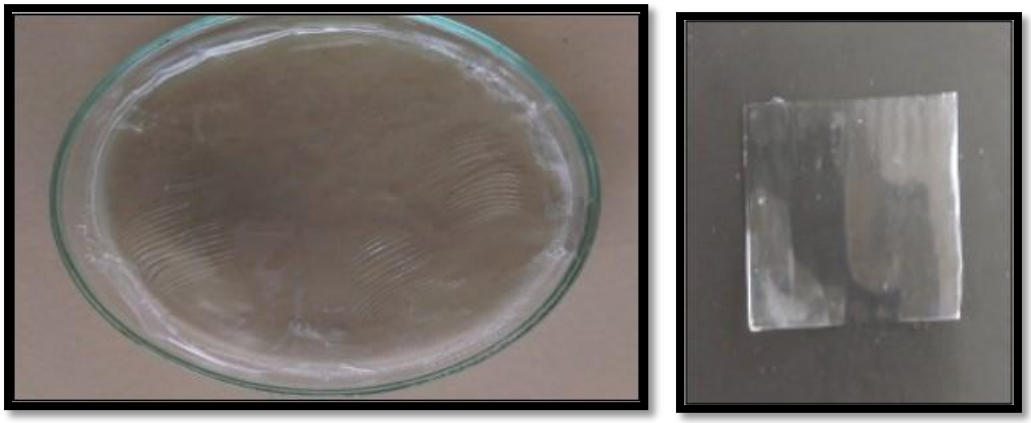


Figure 3: Formulated transdermal patches

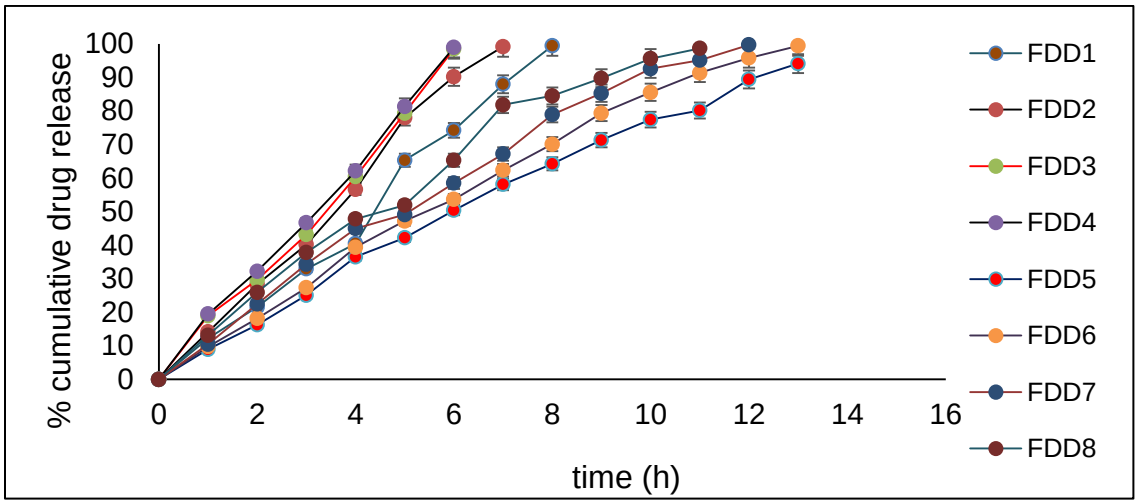


Figure 4: *In vitro* percentage cumulative drug release profile of transdermal patches containing DMSO

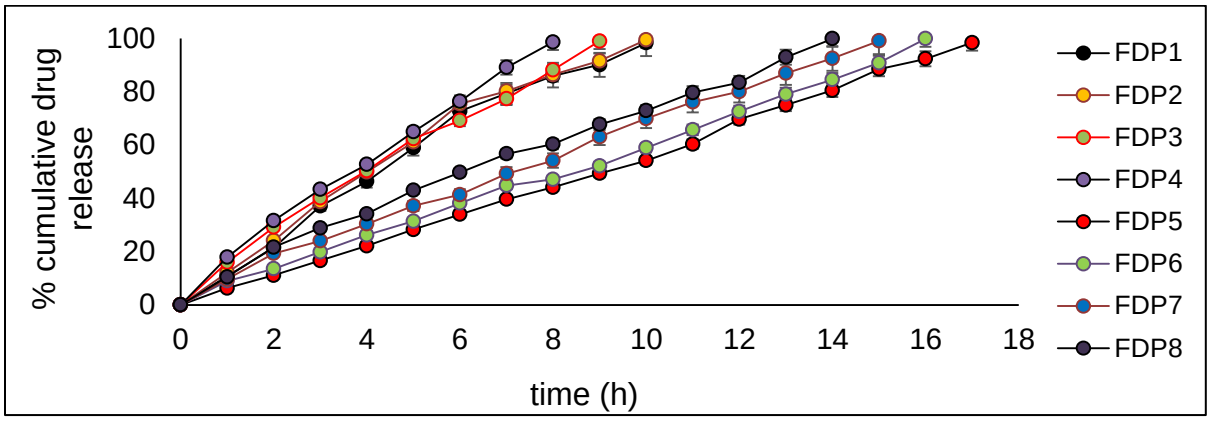


Figure 5: *In vitro* percentage cumulative drug release profile of transdermal patches containing PEG 400

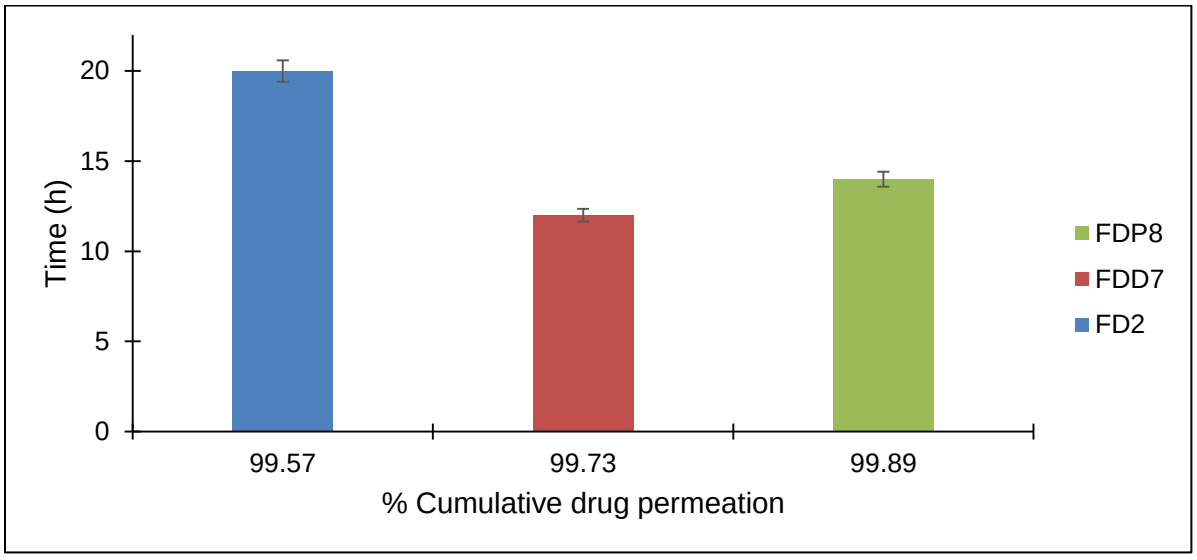
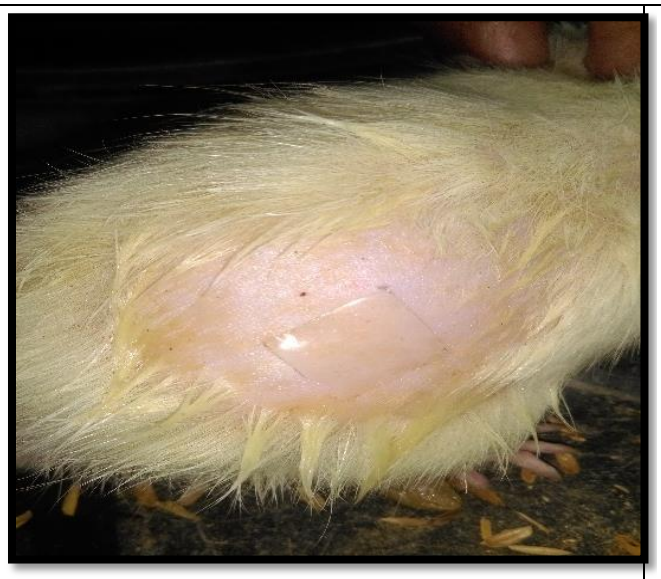
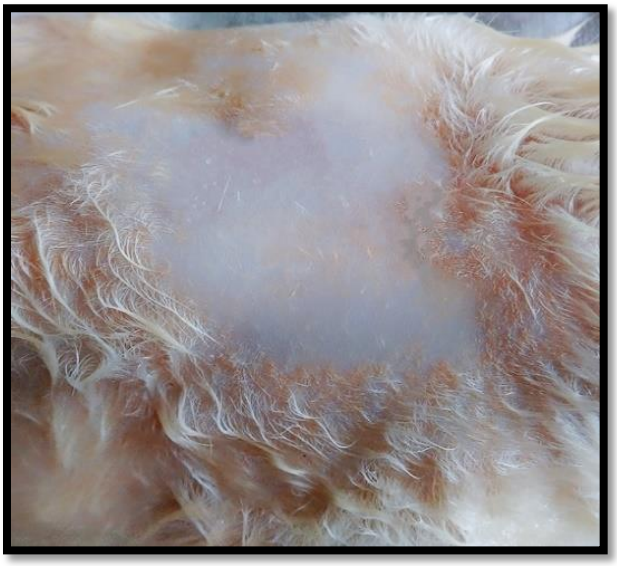


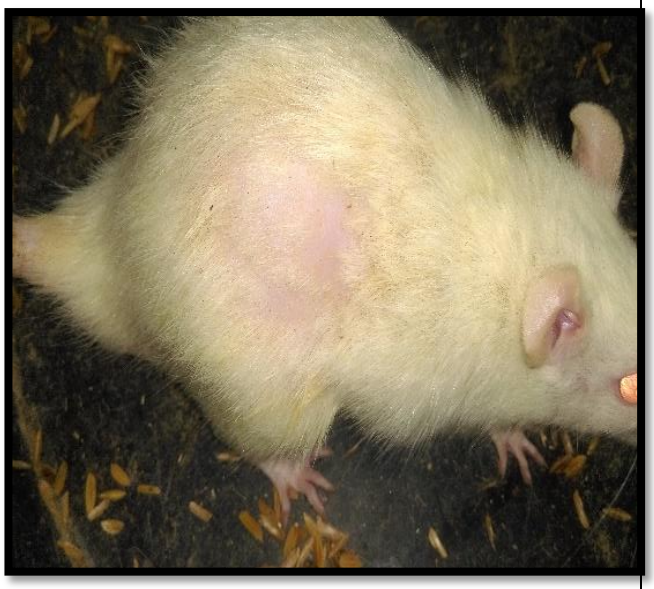
Figure 6: Comparative *in vitro* percentage cumulative drug permeation profile of optimized transdermal patches FD2, FDD7 and FDP8



Albino wistar rat skin condition on application of transdermal patch from 0 h to 12



Albino wistar rat skin condition after 24 h from removal of transdermal patch.



Albino wistar rat skin condition after 48 h from removal of transdermal patch

Albino wistar rat skin condition after 72 h from removal of transdermal patch

Figure 7: *In vivo* skin irritation study

CONCLUSION

Thin, flexible, smooth and transparent films were obtained with PVA using glycerol as plasticizer. Thickness of all formulations remained uniform with low SD values. In order to reduce the dosing frequency, an attempt was made to develop TDDS of flupirtine maleate for 12 h. As the concentration of DMSO increased, the release profile of drug was enhanced. As the concentration of PEG-400 increased, the release profile of flupirtine maleate was enhanced. The results indicated that DMSO improved the release profile of flupirtine maleate when compared to PEG-400. Studies have shown promising results and therefore it can be used as an extended release formulation.

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REFERENCES

1. Chein YW. Oral drug delivery and delivery systems. 3rd ed. Novel drug delivery systems. Marcel Dekker, Inc., New York, 2002;50: p. 139-96.
2. Prausnitz MR, Mitragotri S, Langer R. Current status and future potential of transdermal drug delivery. Nat Rev Drug Discov.2004;3:115-24.
3. Gaur PK, Mishra S, Purohit S, Dave K. Transdermal drug delivery system – A review. Asian J Pharm Cli Res. 2009;2:14-20
4. Kulkarni PV and Keshavayya J. Preparation and evaluation of polyvinyl alcohol transdermal membranes of salbutamol sulphate. Int J Curr Pharm Res.2010:2(2);13-16.
5. Kumar JR, Selvadurai M, Arumugam SD. Formulation and in vitro evaluation of terbinafine HCl transdermal patches. J Pharm Sci Res. 2012;4(6):1840-43.
6. Morrow DI, McCarron PA, Woolfson AD, Donnelly RF. Innovative strategies for enhancing topical and transdermal drug delivery. Open Drug Del J. 2007;1:36-59.
7. Aggarwal G, Dhawan S. Development, fabrication and evaluation of transdermal drug delivery system – A review. Pharmainfo.net. 2009;7(5):48-52.
8. Barhate DS, Patel MM, Sharma SA, Nerkar P, Shankhpal G. Formulation and evaluation of transdermal drug delivery system of carvedilol. J Pharm Res. 2009;2(4):663-65.
9. Guy RH, Hadgrift J. Physicochemical aspects of percutaneous penetration and its enhancement. Pharm. Res. 1988;5:753-58.
10. Jain S, Goswami M, Bhandari A, Arora V. Skin irritation study of intradermal patch of chitosan containing trazodone HCl on rat skin. Int J Res Pharm Bio Sci. 2011;2(3):102-04.