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Formulation and evaluation of *Momordica charantia* fruit extract based transdermal drug delivery against diabetes

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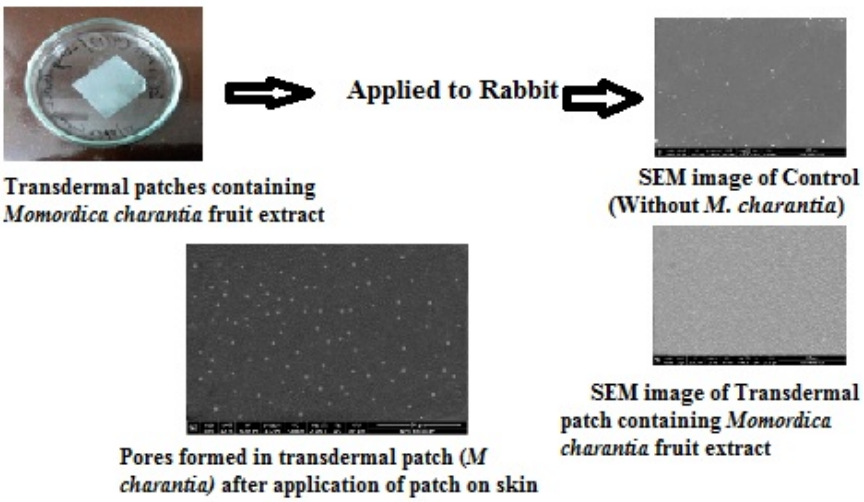
Article

ABSTRACT



Conventional medicine occupies majority of healthcare sector. But slow release and low concentration of these medicines able to reach target site. Transdermal drug delivery system is efficient, easy to use and cost-effective way to deliver medicines to target site. Therefore, present study focuses on developing matrix-type transdermal patches containing *Momordica charantia* fruit extract combined with various polymers. These patches are intended for transdermal drug delivery. Different combinations of polymers, plasticizers, and permeability enhancers were prepared and assessed for various physico-chemical parameters. The release of the drug in rabbit serum was evaluated using High-Performance Liquid Chromatography (HPLC). Additionally, Fourier Transform Infrared (FTIR) analysis was conducted to examine the interaction between the drug and polymers. Scanning Electron Microscopy (SEM) was employed to observe the surface topology of the patches both before and after drug permeation. The formulated patches exhibited favorable physico-chemical properties. FTIR analysis demonstrated compatibility between the drug and polymers. SEM analysis revealed uniform distribution of the drug within the matrix patch, with the presence of permeation holes indicating drug release. Formulation with polymer HPMC (A6) and with a combination of HPMC & Eudragit (A10) displayed enhanced drug release efficiency. In-vitro permeation followed first-order kinetics in ethylcellulose (A1) and HPMC & Eudragit (A10) formulations. Skin tests did not show any signs of erythema. The study's findings suggest that the developed transdermal patches, particularly those containing HPMC and HPMC & Eudragit as polymers, could be a promising option for managing diabetes through systemic drug circulation.

Keywords: Transdermal Drug Delivery system Eudragit Momordica charantia polymer patch Drug delivery

INTRODUCTION

The Transdermal Drug Delivery System (TDDS) is the way to deliver drugs directly via epidermis.[1] The transdermal method aids in increasing drug flux through the skin while reducing drug retention and metabolism.[2,3] The TDDS is a more convenient and effective way than conventional dosage form [4] but still remains unnoticed in its pharmacological relevance.

Transdermal system has emerged as hope against treatment of chronic disease. One such disease is diabetes. Diabetes mellitus is a hyperglycemic disorder brought on by a lack of insulin and often combined with insulin resistance. Currently available therapies have a number of demerits like lack of patient compliance, expensive and not easily accessible. Approximately 220 million individuals are affected by diabetes and probable reason for deaths occur in low- and middle-income countries.[5]

Natural products use is always favored over chemicals due to its cost effective, easy to use, non-toxic, and negligible side-effects. 80% of the world's basic healthcare sector primarily depends on herbal medicine.[6] Hypoglycemic effects of herbs due to its metabolites make it a good alternate agent for reducing glucose level in blood. Efficacious, less side effects in clinical

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experience and relatively low costs are some of the merits associated with herbs. [7] *Momordica charantia* is one such herb. Metabolites present in *Momordica charantia* (bitter melon) have shown the potential against diabetes. [8] Incorporating the herbs or its extract to the transdermal dermal patches for the fast recovery against any disease is a safe and without side-effects approach. With this view, the present research aims to investigate systematically the efficacy, reversibility and dosage form compatibility of polymers along with *Momordica charantia* fruit extract (herbal drug) against diabetes, using *in vitro* and in vivo skin permeation method.

MATERIAL AND METHODS

Polymers

Hydroxy Propyl Methyl Cellulose (HPMC) was benevolently provided by COLORCON Asia Pvt. Ltd, Hyderabad, India; Ethyl Cellulose (EC) was given by Asha Cellulose (I) Pvt. Ltd., Valsad, India; Polyvinylyrrolidone (PVP) gifted by Candila pharmaceuticals limited, Ahmadabad, Gujarat, India; Eudragit gifted by Evonik Degussa India Pvt. Limited, Mumbai, India. All other chemicals like chloroform (used as solvent), dibutylphthalate (used as plastisizer), polyethylene glycol (PEG as penetration enhancer) were of analytical grade. Throughout the investigation, MilliQ water was utilized.

DRUGS

Drug used in the present investigation was fruit powder of *Momordica charantia* purchased from Nutra green, China.

Transdermal patch preparation

PEG (40 percent w/w of dry polymer) and DMSO (10 percent w/w of dry polymer) were included in the formulation of the patches as plasticizers and permeation enhancers, respectively. By varying the ratio EC, HPMC, Eudragit and PVP in different formulations A1, A2, A3, A4, A5, A6, A7, A8, A9, A10 (Table 1), plasticizer, penetration enhancer in 10 ml blend of chloroform. Homogenous solution was prepared using a magnetic stirrer. *Momordica charantia 's* dry extract (50 mg) was slowly poured into the mixture and stirred continuously for 30 minutes to dissolve it. This polymeric solution was poured on moulds with raised edges. [9] The molds were positioned horizontally. Funnel placed over the mould to the rate of evaporation.

Table 1: Preparation of control and bitter melon containing Transdermal Patches

SN	Ingredients	Formulation Code (FC)									
		A1	A2	A3	A4	A5	A6	A7	A8	A9	A10
1	Drug (mg)	-	50	50	50	50	50	50	50	50	50
2	EC (mg)	500	500	250	400	-	-	-	-	-	-
3	PVP (mg)	-	-	-	100	100	-	200	-	100	-
4	HPMC (mg)	-	-	-	-	400	500	300	-	-	200
5	Eudragit (mg)	-	-	250	-	-		-	500	400	300
6	Plasticizer (PEG) % of polymer wt.	40	40	40	40	40	40	40	40	40	40
7	Penetration Enhancer (DMSO) % of polymer wt.	5	5	5	5	5	5	5	5	5	5
8	Chloroform Casting Solvent (10 ml)	$CHCl_3$	$CHCl_3$	$CHCl_3$	$CHCl_3$	$CHCl_3$	$CHCl_3$	$CHCl_3$	$CHCl_3$	$CHCl_3$	$CHCl_3$

After 24 h, prepared films were taken and cut in size of 1.0 cm^2 diameter to generate transdermal patch (Fig. 1). One patch was taken randomly for evaluation and rest were stored in dessicator until further evaluation. Adhesive polymer was applied on outer layer of transdermal patch for proper contact of patch with rabbit skin. [10]

1. Physicochemical Evaluation:

1.1 Thickness: Five different places were selected to calculate thickness using gauze (Instrumentation India) [11] and their mean ± SD values of three readings were calculated.

1.2 Uniformity of weight: This was done by randomly selecting individual patches [12] and their mean ± SD values of three readings were calculated.

1.3 Drug content determination: An accurately weighed patch was added in 100 ml of solvent and in a shaker incubator, the fluid is continually churned for 24 hours. After this complete solution was sonicated and filtered. Filterate was used for spectrophotometric analysis and mean ± SD values of three readings were calculated.

1.4 Moisture content: A transdermal patch of known weight was exposed to 80% relative humidity in a desiccator, and weight until constant weight was observed. The percentage of moisture content was determined using Gupta and and Mukherjee, 2003 [13] and their mean ± SD values of three readings were calculated

$$\% \text{ Moisture content} = \text{Initial weight} - \text{Final weight} \times 100$$

1.5 Flatness: This parameter was computed by slicing one strip from the center of each patch and two strips from each side. Each strip's length was measured, the variance in length was assessed using the percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

$$\% \text{ constriction} = I_1 - I_2 \times 100$$

I_2 = Final length of each strip; I_1 = Initial length of each strip

1.6 Folding Endurance: It was determined by folding one film in the same spot over and over until it broke. [14]

1.7 Surface pH-The patches were kept in 0.5 ml of phosphate buffer saline for 1h. The surface pH was assessed using pH paper. The mean of three readings were recorded. [15]

1.8 Swellability- The drug loaded patch was weighed. After 10 minutes, 50 milliliters of phosphate buffer (pH 7.4) solution were added to the petri dish. The patch was taken off, cleaned

with tissue paper, then weighed repeatedly for up to an hour until a steady weight was noticed. The weight gain is caused by the absorption of water and expansion of the patch due to the difference in weight[16] and their mean ± SD values of three readings were calculated

The percentage swelling was calculated using the following equation-

$\% S = (X_t - X_0/X_0) \times 100$

Where X_t = weight of the swollen patch after time t and

X_0 = original patch weight at zero time.

2. Instrumentation

2.1 FTIR (Fourier Transform Infrared) spectroscopy

Interaction of bitter melon with polymers was analyzed using the FTIR [SHIMADZU]. In a pressure compression machine, 3-5 mg of sample were ground with 100–150 mg of potassium bromide to create the KBr pellet. The bitter melon was put in an FTIR chamber and scanned between 4000 and 400 cm^{-1} in wavelength.

2.2 Scanning electron microscopy- The exterior morphology of bitter melon containing patches was evaluated using a scanning electron microscope (NOVA NANO) at 15.00 kV. Samples were gold coated before scanning so as to make them electrically conductive.

3. *In vitro* drug release:

This parameter was assessed using a Franz diffusion cell. The patch was placed on the glass disc in such a way that their drug matrix towards the dissolution medium (having phosphate buffer pH 7.4). After placing patch at the bottom, paddles were rotated at 50 revolutions per minute. 5 mille liters of solution as samples were used for drug content through a spectrophotometric method. The graph was plotted between cumulative percentage of drug release against time (in hr).

3.1 *In vitro* permeation studies: An *in-vitro* skin permeation study was performed by using a modified Keshary- Chien diffusion cell [17] using hairless rabbit skin. Skin was affixed on KC cell using silicone-gel followed by *in-vitro* experimentation

The receiver compartment temperature was kept at 32±5°C (for skin) and stirred constantly. Withdrawal of sample was carried out at regular interval of time and simultaneously equal amount of buffer was added each time. The sample's absorbance was evaluated spectrophotometrically.

IN VIVO STUDIES

In vivo evaluation provides true information about drug performance. *In vivo* evaluation of durg containing patch was performed using rabbit as model organism. All animal studies were conducted in accordance with Committee for the Purpose of Control and Supervision of Experiments on Animals (Reg. No. 1678/Go/Re/S/12/CPCSEA).

HPLC was performed to analyze the amount of drug permeated in blood after forty-eight hours of patch (A10) application on rabbit abdominal skin. Serum was isolated at 4000 rpm for twenty minutes at 4^0C from the blood sample collected from the marginal ear vein. This sample was used for HPLC (AGILENT INFINITY1200). UV-VIS L-7420 detector with D-7000 interface for HPLC pump was used. Using a C18 column (Chrombudget-Bischoff Chromatography) that was 0.46 x 100 cm long and 5 microns thick, the separation was done. Acetic acid, acetonitrile, and water made up the mobile phases. Water/acetonitrile/acetic acid (94.9/5/0.1 v/v/v) makes up mobile phase A, while water/acetonitrile/acetic acid (5/94.9/0.1 v/v/v) makes up mobile phase B. The flow rate was held at 1 ml/min, the injection volume was 20 l, and the gradient was applied over a period of 25 minutes as follows: for the first 15 minutes, mobile phase A was at 100%; the next 15 to 20 minutes saw a change from 100% to 30% for mobile phase A; and the final five minutes saw a return to 100% for mobile phase A. UV absorbance is used to find effluent. The extraction was carried out with the help of 60% milli Q water. It was then sonicated (4-5 minutes) and kept still for 40 minutes. The supernatant obtained was filtered and injected into the HPLC system.

Skin irritation test- The transdermal formulation was examined in experiments on rabbits for any skin irritancy. One day before use, the dorsal hairs were removed and the skin was well cleansed. To simulate the circumstances of usage, a medicated formulation was applied with adhesive tape and covered with occlusive dressing. After 24 hours, the patch was removed, and the region was examined for any signs of edema or erythema. [18]

RESULTS AND DISCUSSION

In the current study, solvent casting and solvent evaporation techniques were used to create transdermal patches of *Momordica charantia* (bitter melon) fruit extract using a glass mould with a predetermined diameter. (Fig. 1). The monolithic transdermal patches of bitter melon fruit extract were formed using a single or different combination of polymers that gives flexible, smooth and transparent patches. Table 2 displays the composition of several formulations.

Figure 1: Formulation of Patch

Table 2: Physical characterization of transdermal patches of polymer and bitter melon fruit extract (drug)

FC	Physical Appearance	Weight	Thickness	Drug Content	Surface pH	Folding Endurance	Flatness %	Swellability
A1	+++	26.83 ±4.07	0.088 ± 0.007	-	7	> 200	100	1.17 ± 1.92

A 2	++	31.50 ± 4.14	0.080 ± 0.014	95.023 ± 1.762	7	>200	100	0.50 ± 0.43
A 3	+++	25.67 ± 12.29	0.095 ± 0.018	93.728 ± 2.002	7	>200	95	0.17 ± 0.26
A 4	+++	35.67 ± 6.65	0.101± 0.013	96.308 ± 1.114	7	>250	94	1.00 ± 0.47
A 5	++	16.67 ± 6.28	0.121± 0.017	95.12 ± 2.149	7	>150	98	0.833 ± 0.627
A 6	++	16.17 ± 4.40	0.053± 0.008	94.893 ± 1.954	7	>200	96	0.083 ± 0.587
A 7	++	17.08 ± 5.86	0.145 ± 0.013	95.688 ± 2.085	7	>250	98	0.167 ± 0.416
A 8	++	18.87 ± 4.54	0.093± 0.015	95.986 ± 1.003	7	>200	98	0.417 ± 0.103
A 9	++	23.17 ± 3.43	0.090± 0.025	95.338 ± 1.346	7	>200	100	1.000 ± 0.124
A 10	++	35 ± 4.90	0.085± 0.015	96.326 ± 1.339	7	>200	98	0.417 ± 0.103

mean ± SD (n=3)

The weight of different formulation code ranged between 16.17 ± 6.28 mg to 35.13 ± 4.9 mg. Great consistency of medication content among the patches was seen with all and ranged from 94.893 ± 1.954% in A6 to 96.326 ± 1.339% in A10. These results indicate uniform distribution of drug content with minimal variability. The amount of drugs found was in acceptable range (85–105%) for a given area. [19, 20]

The **flatness** study showed the same strip length before and after cuts in all formulations, i.e. there was zero constriction and total flatness. These results indicate stability and appropriate combination of selected polymers. [21, 22]

Folding endurance test results indicated good integrity and showed good strength to withstand unfavorable environment like folding of skin. These results are in agreement with previous work. [20]

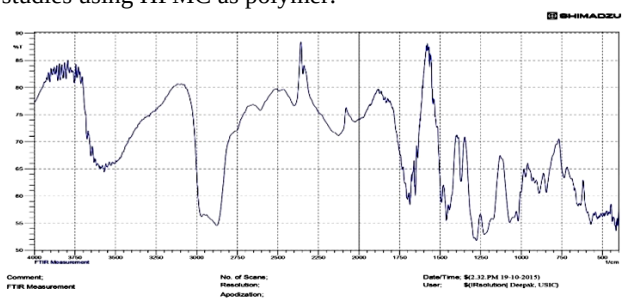
Moisture content of the patches increases proportionally in the concentration of hydrophilic polymer. Prepared patches of different formulations were low in moisture. Thus, help the formulations in long term storage as they remain stable and reduce brittleness. Low in moisture content may be due to hydrophobic polymer. [23]

All formulations' surfaces had a pH of 7.0 value, which indicates that chances of skin irritation is expected to be negligible. Both acidic and basic pH can cause skin irritation. Swellability index was found in range from 0.417 ± 0.103 to 1.17 ± 1.92 which indicates the stability of patch.

Drug-Excipients interactions

FTIR characterization

Both the drug and the drug-polymer combination had nearly similar main peaks to those of pure components, which demonstrated, based on the physical mixture's IR spectra, that the drug and polymer did not interact with one another. Peaks in the spectrum occasionally merged because of the interaction between the polymer and medication. These findings suggested that an amorphous form of the bitter melon transdermal patch might be present. The FTIR spectra demonstrated that the principal drug bands were intact and that there was no indication of a contact, demonstrating the compatibility of drugs with polymers (Fig. 2 and 3) (Table 3, 4 & 5). Similar results were obtained in other studies using HPMC as polymer. [24]



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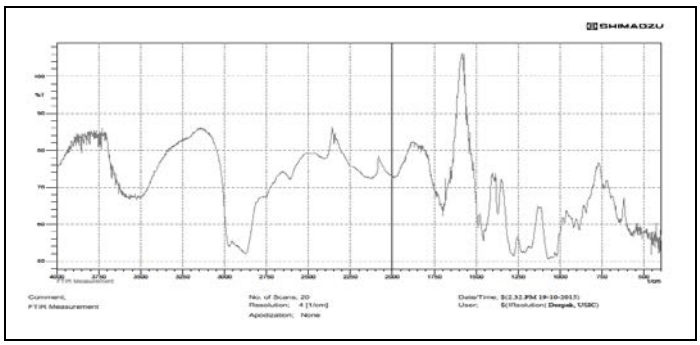

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Figure 2: A. FTIR peaks for Ethylcellulose B. FTIR peaks for ethylcellulose and Bitter melon

Table 3: Infrared spectral assignment

Sr.No.	Frequency(cm-1)	Vibration Mode
1.	3600-3500	Amine N-H Stretch
2.	2900-2750	Carboxylic Acid O-H Stretch
3.	1750-1650	Aromatic C=C Bending
4.	1300-1250	Carboxylic Acid O-H Stretch
5.	850-750	Aromatic C-H Bending

Table 4: Infrared spectral assignment

Sr.No.	Frequency(cm^{-1})	Vibration Mode
1.	3000-2850	Carboxylic Acid O-H Stretch
2.	2650-2500	Carboxylic Acid O-H Stretch
3.	1750-1650	Aromatic C=C Bending
4.	1000-850	Amide C=O Stretch
5.	750-600	Aromatic C-H Bending

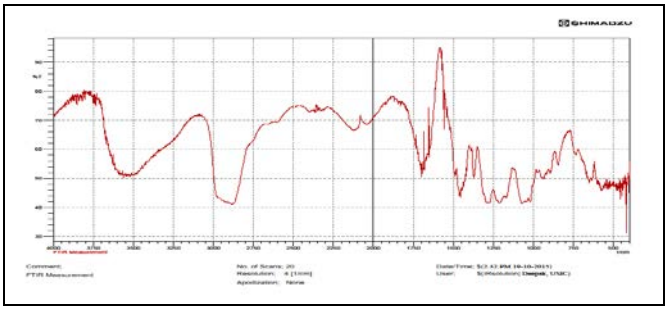


Figure 3: FTIR peaks for HPMC

Table 5: Infrared spectral assignment

Sr.N.	Frequency(cm^{-1})	Vibration Mode
1.	2900-2850	Carboxylic Acid O-H Stretch
2.	1700-1650	Aromatic C=C Bending
3.	1500-1450	Amide C=O Stretch
4.	1050-1000	Alkynyl C-H Stretch
5.	700-650	Aromatic C-H Bending

Scanning Electron Microscopy (SEM)

Uniform distribution of the drug increases its repeatable rate of release from a specific location when patch applied to the skin. Under in vivo conditions, the surface topography of the transdermal patches was examined both before and after the medication from the patches permeated the skin (Fig. 4) revealed that the medication was evenly distributed across the matrix patch before penetration [25] and following skin permeation, as evidenced by the number of holes. [26]

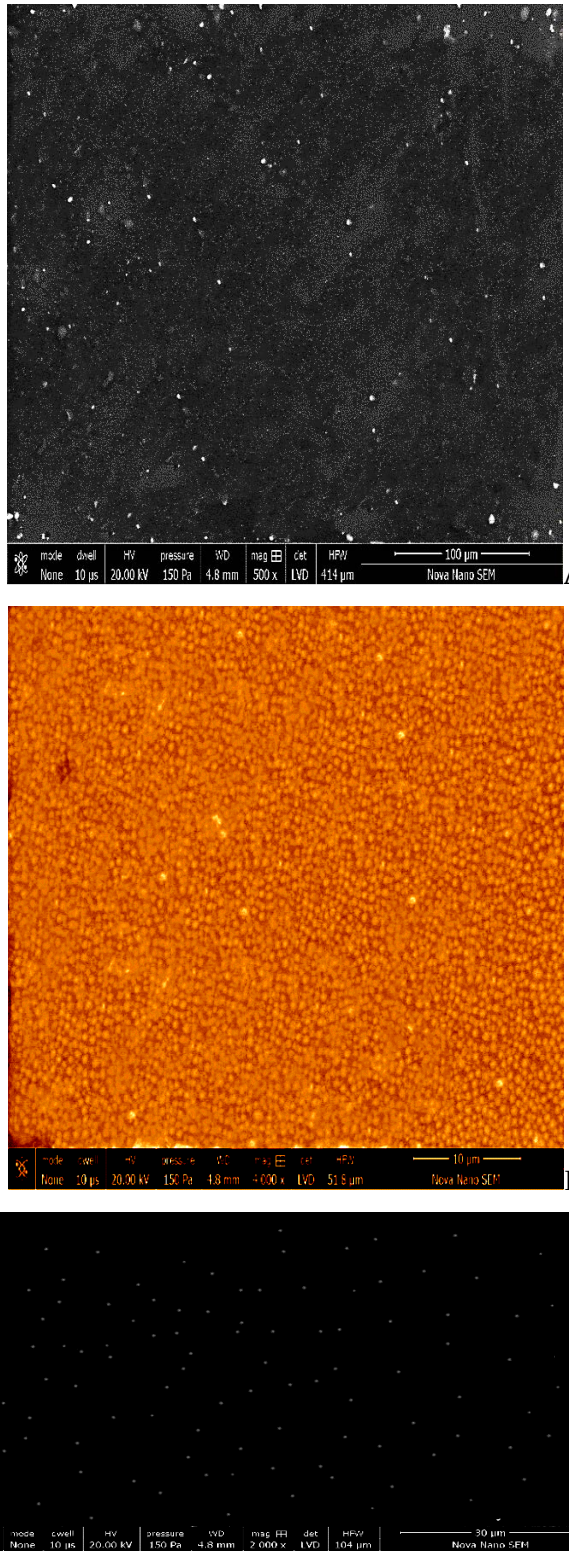


Figure 4 A: Control (Without Drug) B: Transdermal patch containing *Momordica charantia* fruit extract C: Pores formed in transdermal patch containing *Momordica charantia* fruit extract after application of patch on skin showing absorption of drug from patch

IN VITRO DRUG RELEASE

In a phosphate buffer at a pH 7.4 for 12 hours, dissolution studies were conducted. The samples were assessed using a UV spectrophotometer, results indicate that the formulation A10 (HPMC and Eudragit) and A6 (HPMC) alone are more efficient in drug release for a prolonged span of time as shown in Fig. 5. HPMC polymer is sparingly soluble in water and Eudragit also solubilizes very slowly in water may be the reason for slow and long constant release of drug.

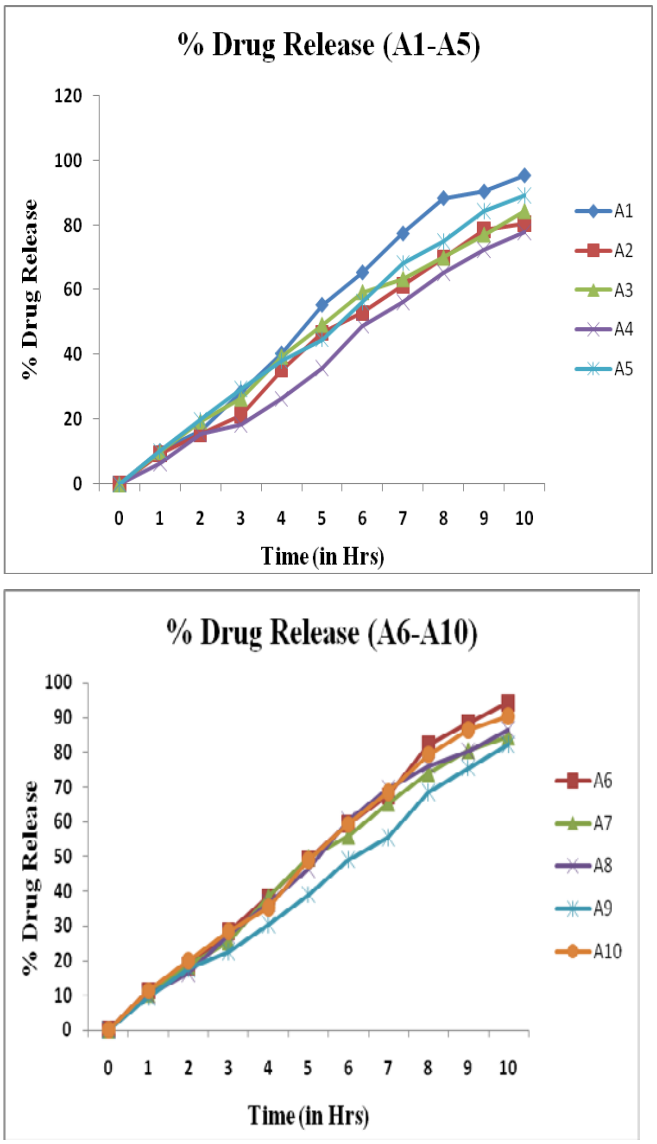


Figure 5: Percentage drug release of formulation A1 to A10

IN VITRO SKIN PERMEATION

In-vitro permeation studies of formulations were performed by a using modified Keshary-Chien diffusion cell that showed first order kinetics with A1 (ethyl cellulose) formulation and A10 (HPMC & Eudragit combination). The permeation of drug through these polymers was found to be higher than other formulations in case of *Momordica charantia* (Fig. 6). These results may be due to interaction of polymers with penetration enhancers which promote slow and sustained release of drug. Further, similar results were obtained with Eudragit polymer. [27,28] Further, the hydrophilic nature of HPMC could be a probable reason for sustained permeation as shown in earlier work. [29]

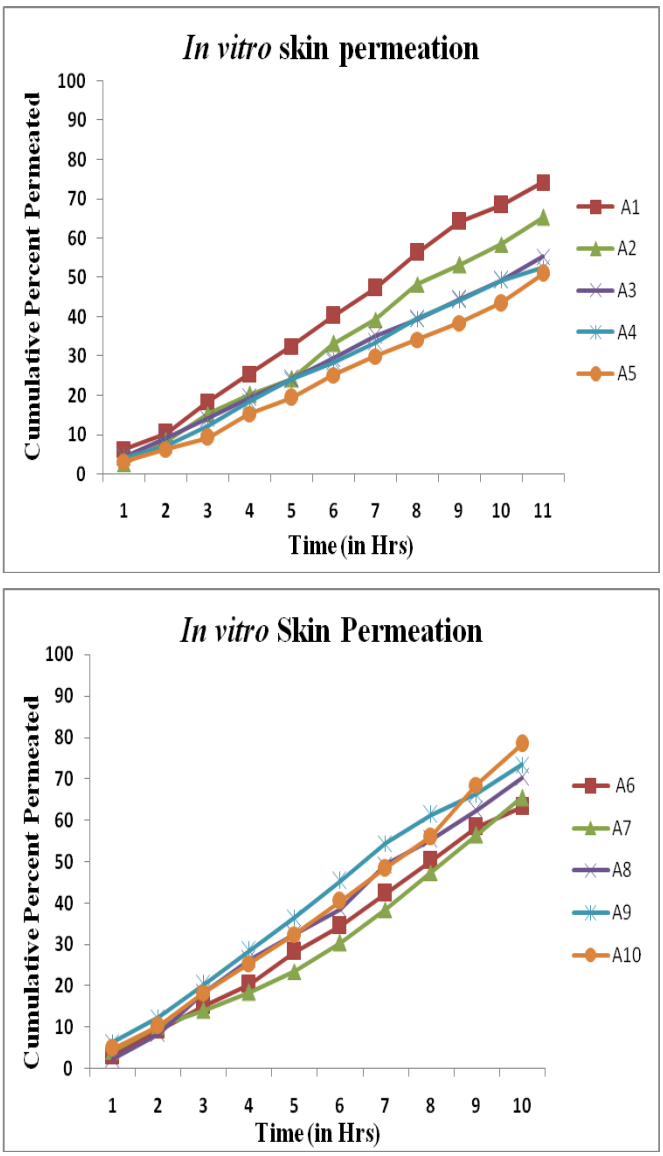


Figure 6 : *In vitro* skin permeation of formulation A1 to A10

SKIN IRRITATION

Skin irritation test of different patch formulations were performed to check any irrational effect on rabbit skin. Patches showed no sign of erythema and free from skin irritant after forty-eight hour's application on abdomen of rabbit (Fig. 7). [30] De-haired area allows maximum contact with skin and helps to analyze impact of formulated patches. Slight edema was observed with A1 formulation.

The planned approach has been validated based on the experiments conducted during validation using stigmasterol and

quercetin as standard for bitter melon fruit extract. The precision and accuracy levels were judged to be within acceptable ranges. LQC, MQC, and HQC all showed consistent recoveries (lower, intermediate and higher quality control samples respectively). Stock (stable at 4 °C for 10 days) and working standard (stable for 6.00 h) stability were evaluated for both short-term (6 h) and long-term effects (10 days) [Fig. 8 and Table 6].

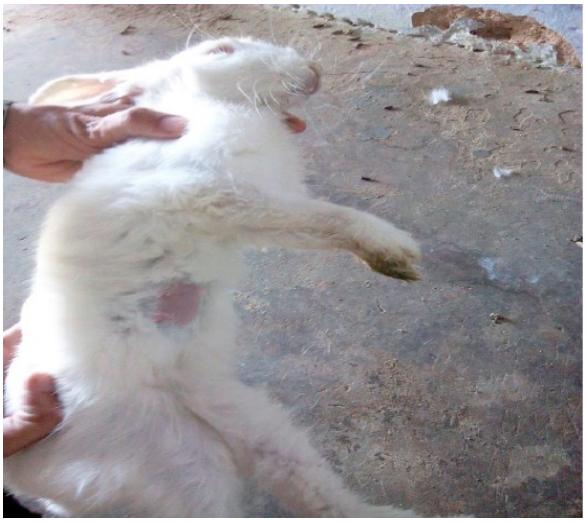
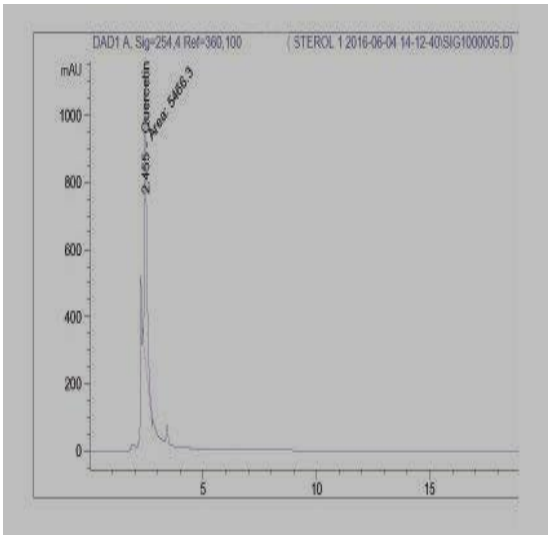


Figure 7: No sign of erythema was observed

The objective of current research was to develop a matrix-type transdermal patches containing herbal drug i.e. *Momordica charantia* fruit extract (50 mg) with different ratios of polymeric systems diabetic rabbits. Formulations containing HPMC and HMPC & Eudragit polymer with *M. charantia* fruit extract showed encouraging outcomes. Thus, *Momordica charantia* fruit extract may be a viable option for the effective and controlled administration of diabetes medication into the systemic circulation in a natural and healthy manner.



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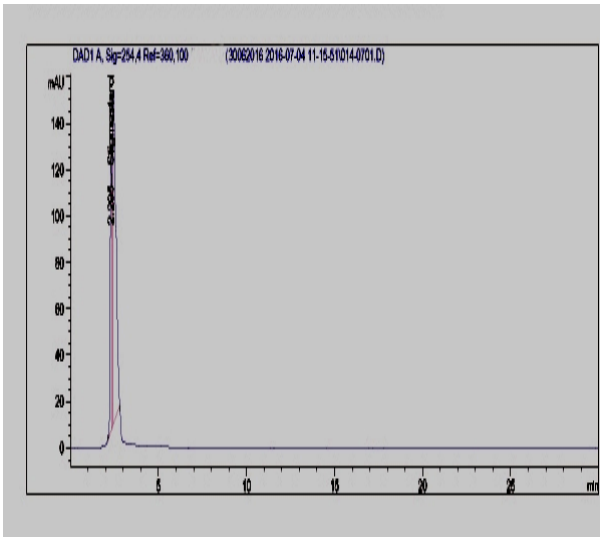

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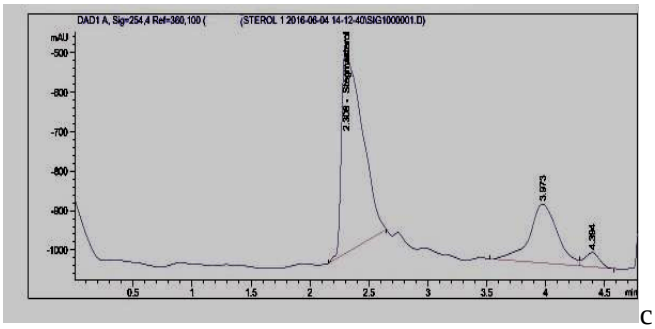

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Figure 8: Representative HPLC chromatograms (a) standard Querestin (b) Standard Stigmasterol and (c). *Momordica charantia* fruit extract in serum

Table 6: Method validation parameters

Parameters	Results
LOD (ng/mL)	5.0
LOQ (ng/mL)	50
Linear range (ng/mL)	100–8000
Mean correlation coefficient (*r*2)	0.9967
Mean slope	22.412
System suitability (% CV, *n* = 5)	
Retention time	0.13
Area	1.05
Precision (% CV, *n* = 3)	
Within-batch	1.14–1.73
Between-batch	1.69–1.96
Recovery (%, *n* = 7)	
LQC	101.80
MQC	99.24
HQC	98.67
Stability	
Long-term stability	
Standard stock solution stability (for 10 days)	Stable at (4 ± 1°C)
Short-term stability	
Bench top stability (For 6.00 h)	Stable at (25 ± 2°C)
Autosampler stability (For 12.00 h)	Stable at (4 ± 1°C)

CONCLUSIONS

The objective of current research was to develop a matrix-type transdermal patches containing herbal drug i.e. *Momordica charantia* fruit extract (50 mg) with different ratios of polymeric systems diabetic rabbit. Formulations containing HPMC and HMPC & Eudragit polymer with *M. charantia* fruit extract showed encouraging outcome. Thus, *Momordica charantia* fruit extract have great utility and may be a viable option for effective and controlled release of drug in to the systemic circulation to manage diabetes in healthy and herbal way.

ACKNOWLEDGMENTS

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