ejpmr, 2016,3(5), 556-569

SJIF Impact Factor 3.628

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

FORMULATION AND EVALUATION OF MATRIX TYPE TRANSDERMAL THERAPEUTIC SYSTEM CONTAINING GLIBENCLAMIDE

Santosh Girani*[1], Dhaval Patel[2], Mantesh Kavatekar[3], Ajay Shahapur[4] and Vital Vijapure[5]

[1,2,3,4]Department of Pharmaceutical Technology B.L.D.E.A's College of Pharmacy Bijapur, Karnataka, India.
[5]Department of Pharmaceutics B.L.D.E.A's College of Pharmacy B.L.D.E.A's, Hospital Campus Bijapur, Karnataka, India.

***Corresponding Author: Santosh Girani**

Department of Pharmaceutical Technology B.L.D.E.A's College of Pharmacy Bijapur, Karnataka, India.

Article Received on 17/03/2016 **Article Revised on 05/04/2016** **Article Accepted on 26/04/2016**

ABSTRACT

The purpose of this research was to develop a matrix-type transdermal therapeutic system containing drug Glibenclamide with different ratios of polymeric (Eudragit RS100, Ethyl cellulose, Hydroxypropyl Mehyl cellulose) systems by the solvent evaporation technique by using 30% w/w of di-butyl phthalate to the polymer weight, incorporated as plasticizer. The physicochemical compatibility of the drug and the polymers studied by infrared spectroscopy suggested absence of any incompatibility. Formulated transdermal films were physically evaluated with regard to thickness, weight variation, drug content, folding endurance moisture. All prepared formulations indicated good physical stability. In-vitro permeation studies of formulations were performed by using Franz diffusion cells. It shown that drug release follows zero order and the mechanism of release is diffusion from the polymer.

KEYWORDS: Glibenclamide, Eudragit RS100, Ethyl cellulose, Hydroxypropyl Mehyl cellulose, Transdermal Film. In-vitro permeation study.

INTRODUCTION

Transdermal drug delivery is one of the most promising methods for drug application. Increasing numbers of drugs are being added to the list of therapeutic agents that can be delivered to the systemic circulation via skin.[1] The main advantages of this system are that there is controlled release of the drug and the medication is painless. The drug is mainly delivered to the skin with the help of a transdermal patch which adheres to the skin.[2] The transdermal drug delivery system has potential advantages of avoiding hepatic first pass metabolism, maintaining constant blood level for longer period of time resulting in a reduction of dosing frequency, improved bioavailability, decreased gastrointestinal irritation that occur due to local contact with gastric mucosa and improved patient compliance.[3] The transdermal patch was approved in 1981 to prevent the nausea and vomiting associated with motion sickness, the FDA has approved, more than 35 transdermal patch product, spanning 13 moleccules.[4]

Glibenclamide is a potent oral sulfonylurea hypoglycemic agent. It is currently available for treating hyperglycemia in Non insulin dependent Diabetes Mellitus(NIDDM-type-2). The drug inhibiting ATP sensitive K^+ chennels in pancreatic beta cells. This inhibition caused cell membrane depolarisation, opening of voltage dependant Calcium channels thus triggering. Glibenclamide (M.W. 494.004g/mol) and negligible skin degradation.

Plasma half life is 4-6hrs. Which make frequent dosing necessary to maintain therapeutic blood level of the drug a long term treatment. Therefore controlled released Transdermal preparation of Glibenclamide was prepare to give sustain effect as compared to conventional multiple oral dosing.[5]

It is highly accepted that membrane controlled transdermal systems have the distinct advantage that the drug release rate, which is regulated by permeation through the rate controlling membrane, remain relatively constant as long as drug loading in the reservior is maintained at high level.[6] Hence, the proposed work involves the development and evaluation of transdermal drug delivery systems containing Glibenclamide.

MATERIALS AND METHODS

glibenclamide was obtained as gift sample from Miracle pharma. Pvt. Ltd, Mumbai, india. Eudragit RS100 & Ethyl cellulose was procured from Loba Chemical Pvt. Ltd. Mumbai. other excipients used were of standard pharmaceutical grade and all chemical reagents used were of analytical grade.

Estimation of Glibenclamide

The spectrophotometric method used in the study was based on the measurement of absorbance at 229 nm, in phosphate buffer pH 7.4.

CALIBRATION CURVE OF GLIBENCLAMIDE

Preparation of Reagents and Solutions

- Preparation of pH 7.4 Buffer.

Place 50 ml of 0.2 M Potassium Dihydrogen Phosphate in a 200 ml of 0.2 M sodium hydroxide and then add water to volume.

- Preparation of 0.2M Potassium Dihydrogen Phosphate

27.218g of Potassium dihydrogen phosphate was dissolved in 1000ml of water.

- Preparation of 0.2M Sodium Hydroxide

8g of Sodium hydroxide was dissolved in 1000ml of water.

Determination of λmax of Glibenclamide in pH 7.4 buffer

Stock solution (100µg/ml) of Glibenclamide was prepared in phosphate buffer pH 7.4. This solution was appropriately diluted to obtain a concentration of 10µg/ml. The resultant solution was scanned in the range of 200nm to 360nm on Elico SL -159 UV-Visible spectrophotometer. The drug exhibited a λmax at 229.0nm in phosphate buffer pH 7.4.

PREPARATION OF STANDARD CALIBRATION CURVE OF GLIBENCLAMIDE IN pH 7.4 PHOSPHATE BUFFER

10mg of Glibenclamide was accurately weighed and dissolved in 100ml of phosphate buffer pH 7.4 (SS – I) to get a concentration of 100ìg/ml. From the stock solution- I, aliquots were taken and suitably diluted with phosphate buffer pH 7.4 to get concentrations in the range of 2 to 20 microgram/ml.

The absorbance of these samples were analyzed by using UV-Visible Spectrophotometer at 229.0nm against reference solution Phosphate buffer pH 7.4.

The Linear Regression Analysis

The linear regression analysis was done on Absorance values. The standard calibration curve obtained had a Correlation Coefficient of 0.9995 with of slope of 0.0143 and intercept of 0.003. A straight line equation (**y = mx + c**) was generated to facilitate the calculation of amount of drug. The equation is as follows.

Absorbance = 0.0143 X Concentration + 0.003

FORMULATION STUDIES

PREPARATION OF TRANSDERMAL PATCH

Mercury substrate method

The polymers, Eudragit S100, Ehyl cellulose (EC) and Hydroxy Propyl Methyl Cellulose(HPMC) were taken in required quantity as shown in the table. About 10 ml of solvent mixture of Chloroform: methanol (4:1) was added and shaked to prevent the formation of lumps, and then kept aside for swelling of polymers. And after complete solublization of polymers in mixture of solvent, added required quantity of dibutyl phthalate to this mixture, and vertexed.

Finally weighed quantity of Glibenclamide added to the polymer solution and mixed well. It was set-aside for some time to exclude any entrapped air and was then transferred into a previously cleaned Petri dish (70 cm2) and then this was kept aside for solvent evaporation. The rate of solvent evaporation was controlled by inverting a glass funnel over the petri plate. After overnight, the dried films were taken out and stored in a dessicator.[7]

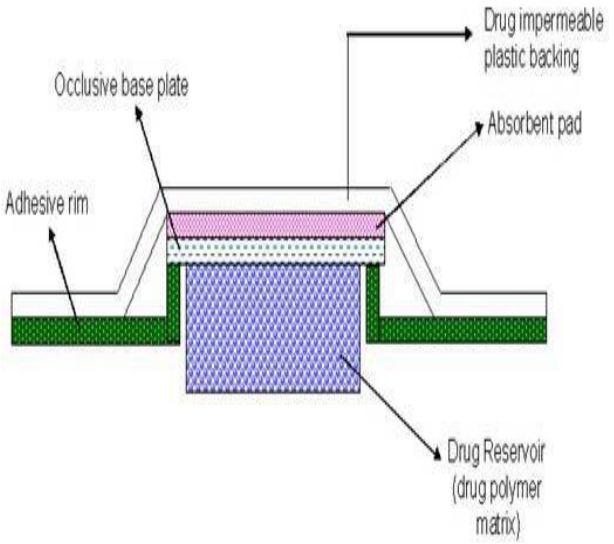

Fig. No: 1. Matrix Diffusion–Controlled Systems.

Table. No. 1: Formulation trials of Glibenclamide Patches.

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8
Glibenclamide (mg)	100mg	100mg	100mg	100mg	100mg	100mg	100mg	100mg
Eudragit RS100 (mg)	400mg	-	300mg	200mg	100mg	200mg	-	300mg
Ethyl cellulose (mg)	-	400mg	100mg	200mg	300mg	-	200mg	-
HPMC (mg)	-	-	-	-	-	200mg	200mg	100mg
DBP (ml)	30%	30%	30%	30%	30%	30%	30%	30%
Chloroform (ml)	8ml	8ml	8ml	8ml	8ml	8ml	8ml	8ml
Methanol (ml)	2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml

EVALUATION OF TRANSDERMAL PATCHES

The prepared transdermal system were evaluated for,

- Physical appearance
- Thickness uniformity
- Weight uniformity
- Folding Endurance
- Drug content uniformity
- Fourier transform infrared spectroscopy
- Differential scanning colorimetry
- Water vapour transmission
- Tensile strength
- Swelling index
- In-vitro drug release study
- Skin irritation study
- Stability studies.

Physico-Chemical Evaluation

- **Physical appearance**

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

- **Thickness of the patch**

The thicknesses of the drug-loaded polymeric films were measured at five different points using a digital micrometer. The average and standard deviation of five reading were calculated for each film.

- **Folding endurance**

The folding endurance measured manually for the prepared film. A strip of film is cut evenly and folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gives the exact value of folding endurance.

- **Weight uniformity**

The films of different batches were dried at 60◦ C for 4 hours before testing. Five patches from each batch were accurately weighed in a digital balance. The average weight and the standard deviation values were calculated from the individual weights.

- **Determination of drug content in the patches**

A fabricated film was cut into small pieces and put in a 100ml of phosphate buffer 7.4 pH solution. This is then stirred in a mechanical stirrer to get a homogenous solution and filtered. The filtrate of 1ml was withdrawn and made up to 100ml, again from this 1ml of solution was pipette out and made up to 10ml with buffer 7.4 pH. The drug content was analyzed at 229nm by UV spectrophotometer.

- **Fourier transform infrared spectroscopy**

The sample were crushed with KBr to make pellets under hydraulic pressure of 600 kg, and then the FTIR spectra were recorded between 400 and 4000 cm^{-1}.

- **Differential scanning calorimetric analysis**

The samples were heated from 0-300 ^{o}C at a heating rate of 10 ^{o}C/min under argon or nitrogen atmosphere using a microcalorimeter (DuPont-9900, USA) and then thermograms were obtained.

- **Water vapour transmission rate:**

Glass vials of 5 ml capacity were washed thoroughly and dried to a constant weight in an oven. About 2 g of fused calcium chloride was taken in the vials and the polymer films of 2.25 cm2 were fixed over the brim with the help of an adhesive tape. Then the vials were weighed and stored in a humidity chamber of 80-90 % RH condition for a period of 24 h 7, 23. The vials were removed and weighed at 24 h time intervals to note down the weight gain.

$$\text{Transmission rate} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Time} \times \text{Area}} \times 100$$

- **Tensile strength**

The films were evaluated using a texture analyzer equipped with a 500 gm load cell. Film strip in 10 cm x 10 cm of dimension and free from air bubbles or physical imperfections, was held between two clamps positioned at a distance of 1 cm.

During measurement, the film was pulled by top clamp at a rate of 100 mm/minutes (ISI Standard speed) and force was applied (using 10kg load cell) gradually till the film was broken. The tensile strengths of 3 films for each formulation were taken directly from the dial reading in kilograms and extension value was also taken directly from the dial reading in mm. The tensile strength at break was calculated as below.

Tensile strength (kg/mm2) =Breaking force (kg)/ cross section area of sample (mm2)

- **Swelling Index**

Weighed pieces 1x1 cm2 of film were immersed in distilled 7.4 phoshphate buffer; at 5, 10, 30, 60min. Soaked films were removed from the medium at predetermined time, blotted to remove excess liquid and weighed immediately. The swelling index was calculated from the weight increase, as follows.

Swelling Index = (W2-W1)/ W1

Where, W1 and W2 are the weight of the film before and after immersion in the medium, respectively.

- **In vitro drug diffusion studies**

The in vitro diffusion study was carried out with the abdominal rate skin using Franz diffusion cell. The cylinder consists of two chambers, the donor and the receptor compartment. The donor compartment was open at the top and was exposed to atmosphere. The temperature was maintained at 37 ± 0.5o C and receptor compartment was provided with sampling port. The diffusion medium used was phosphate buffer (pH 7.4). The diffusion studies were done to get an idea of permeation of drug through barrier from the transdermal

system. In vitro studies are also done for TDDS development. Usually, two types of diffusion cells are used as horizontal and vertical. The Franz and Keshary Chien (K-C) type of diffusion cells are of horizontal type of cells. In this work, K-C type of diffusion cell was used. Diffusion cells generally comprise two compartments, one containing the active component (donor compartment) and the other containing receptor solution (receptor compartment), separated by barrier i.e. albino rate abdominal skin.

The cell consisted of sampling port and temperature maintaining jacket. The outlet and inlet was connected with latex tube so the jacket had stagnant water inside and heat was provided by hot plate.

The stainless steel pin was used to stir the receptor solution using magnetic stirrer. The mice abdominal skin was placed on receptor compartment and both compartments held tight by clamps. Phosphate buffer pH 7.4 was used as receptor solution.

The volume of diffusion cell was 15 ml and stirred with bent stainless steel pin. The temperature was maintained at 37 ± 2°C with the help of magnetic stirrer. The diffusion was carried out for 24 hours and 1 ml sample was withdrawn at an interval of 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 hour. The same volume of phosphate buffer pH 7.4 was added to receptor compartment to maintain sink conditions and the samples were analyzed at 229nm in UV spectrophotometer.

- **Skin irritation test**

The primary skin irritation test was performed on a rabbit weighing between 3-5 kg. Adhesive type USP, was used as a control patch. The trandermal film of 2 cm^2 area was used as test patch.

The test was conducted on an un- abraded skin of the rabbit, where as the patch was placed on the identical site, on the right and left dorsal surface of the rabbit. The films were removed after a period of 24 hrs with the help of alcohol swab. The skin was examinated for erythema/odema.

RESULTS

TABLE 2: Spectroscopic data for the estimation of glibenclamide in phosphate 7.4 buffer pH 7.4 concentration(µg/ml).

Concentration (mcg/ml)	Absorbance
0	0
1	0.080
2	0.145
3	0.218
4	0.282
5	0.350

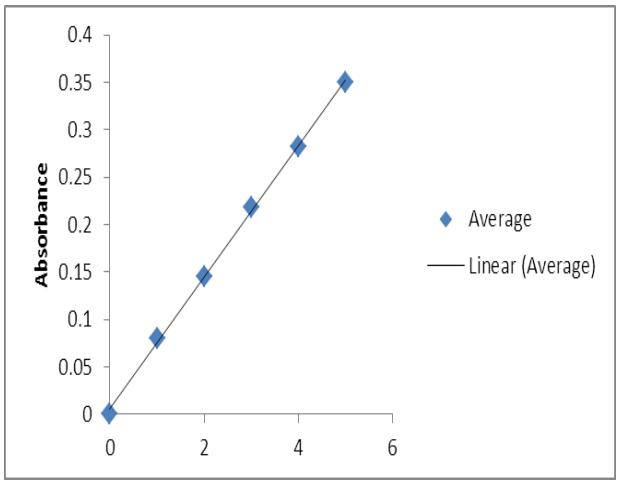

Fig 2.: Calibration curve of Glibenclamide in phosphate buffer pH 7.4.

SLOPE- 0.0143, R^2 – 0.9995.

Physical Appearance

Table.no.5. Physical Appearance.

Sl.no	Formulation code	Appearance
1	F1	++
2	F2	++
3	F3	++
4	F4	++
5	F5	++
6	F6	+-
7	F7	+-
8	F8	+-

++ indicates Satisfactory

+_indicates not Satisfactory

Thickness, Film weight, Folding endurance of Transdermal patches F1 to F8.

Table.no.4

Sl.no	Formulation code	Thickness (mm)±SD	Film weight (mg)±SD	Folding Endurance
1	**F1**	0.231	482	>300
2	**F2**	0.187	434	>300
3	**F3**	0.186	320	>300
4	**F4**	0.193	526	>300
5	**F5**	0.187	389	>300
6	**F6**	0.260	598	>250
7	**F7**	0.292	598	>250
8	**F8**	0.289	508	>300

Percentage Drug content of Transdermal patch F1 to F8.
Table.no.5.

Sl.no	Formulation code	% of drug present AM±SD*
1	F1	94.99%
2	F2	92.30%
3	F3	92.93%
4	F4	91.34%
5	F5	89.11%
6	F6	85.91%
7	F7	82.63%
8	F8	87.19

FTIR

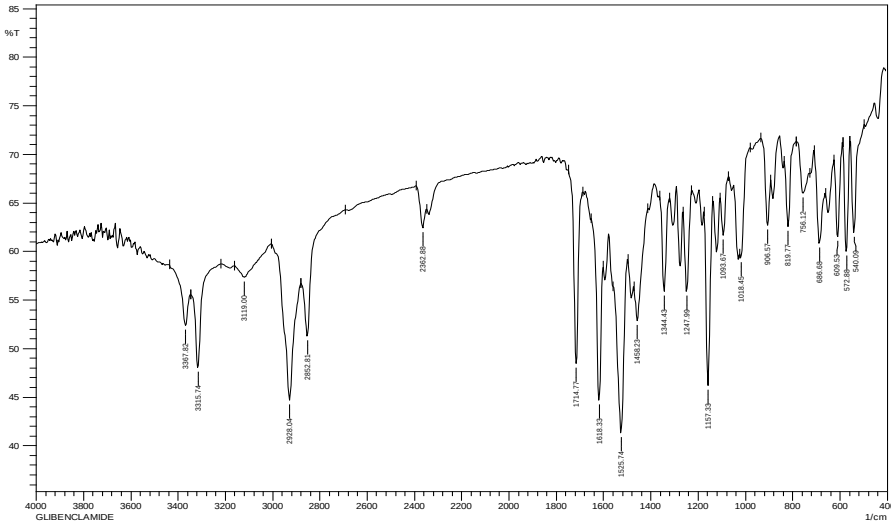

FIG 3- FT-IR OF PURE DRUG GLIBENCLAMIDE

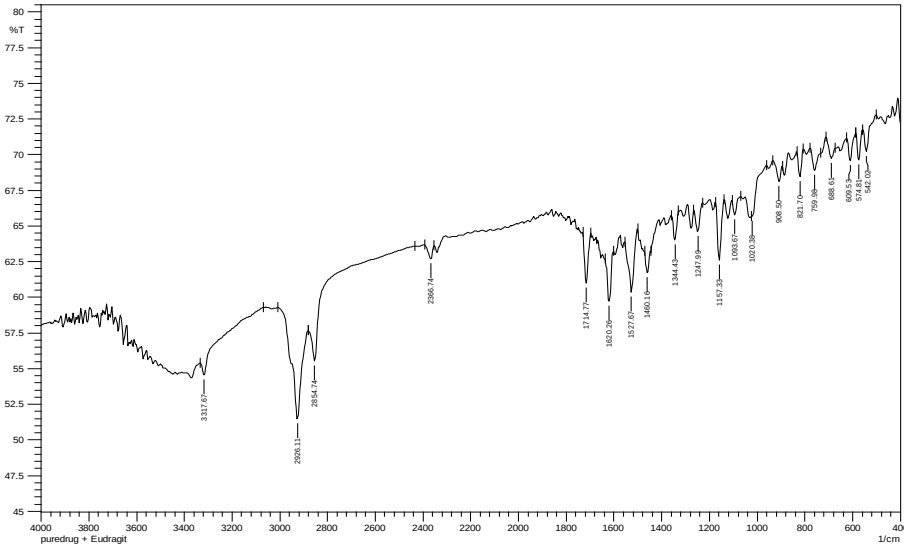

FIG.4 - FT-IR OF PURE DRUG GLIBENCLAMIDE + EUDRAGIT RS-100

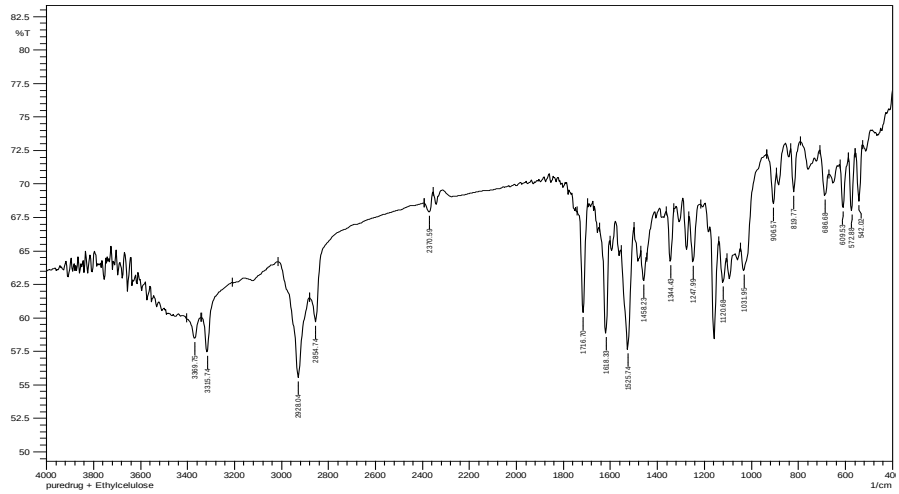

FIG.5- FT-IR OF PURE DRUG GLIBENCLAMIDE + ETHYL CELLULOSE

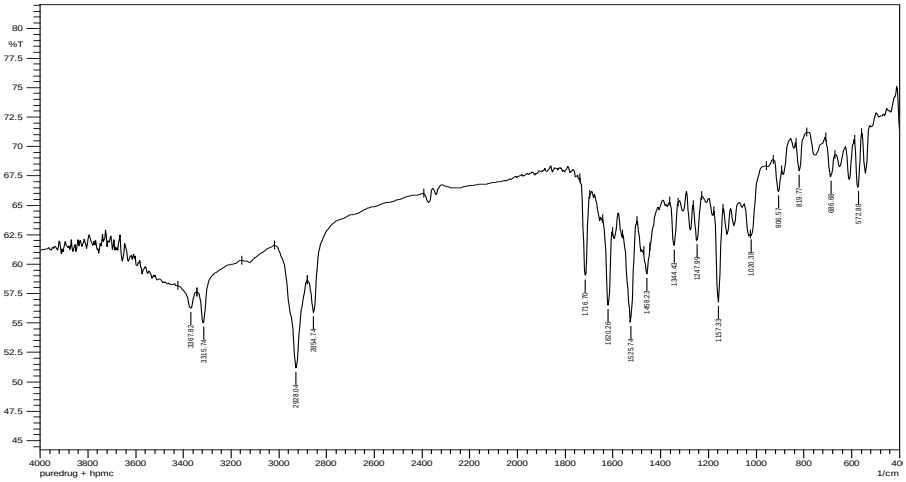

FIG.6 - FT-IR OF PURE DRUG GLIBENCLAMIDE + HPMC

	DSC	Temperature Program:					Comment:	
e:	DRUG GLIBENCLAMIDE		Cel	Cel	Cel/min	min	s	Operator: BVCOP
ent Date:	9/19/2013	1*	30	305	10	0	0.5	Gas1: N2
ame:	DRUG GLIBENCLAMIDE							Pan: Al
eight:	10.000 mg							
e Name:	ALUMINA							
e Weight:	10.000 mg							

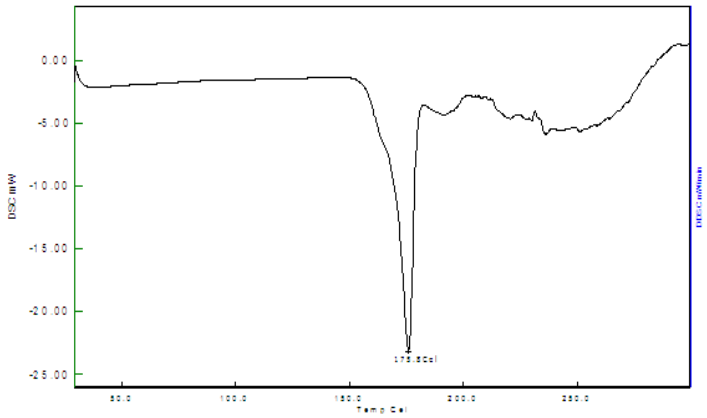

FIG 7: DSC curve of pure drug glibenclamide

::	DSC	Temperature Program:						Comment:	
lame:	DRUG LOADED PATCH F1		Cel	Cel	Cel/min	min	s	Operator: BVCOP	
ement Date:	9/23/2013	1*	30	305	10	0	0.5	Gas1: N2	
Name:	DRUG LOADED PATCH F1							Pan: Al	
Weight:	10.000 mg								
nce Name:	ALUMINA								
nce Weight:	10.000 mg								

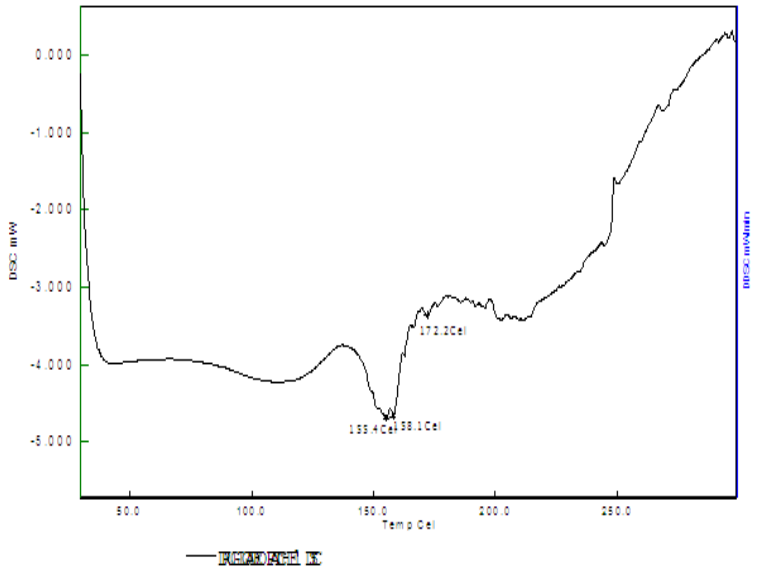

FIG 8: DSC curve of pure drug loaded patch F1

::	DSC	Temperature Program:						Comment:	
lame:	DRUG LOADED PATCH F2		Cel	Cel	Cel/min	min	s	Operator: BVCOP	
ement Date:	9/23/2013	1*	30	305	10	0	0.5	Gas1: N2	
Name:	DRUG LOADED PATCH F2							Pan: Al	
Weight:	10.000 mg								
nce Name:	ALUMINA								
nce Weight:	10.000 mg								

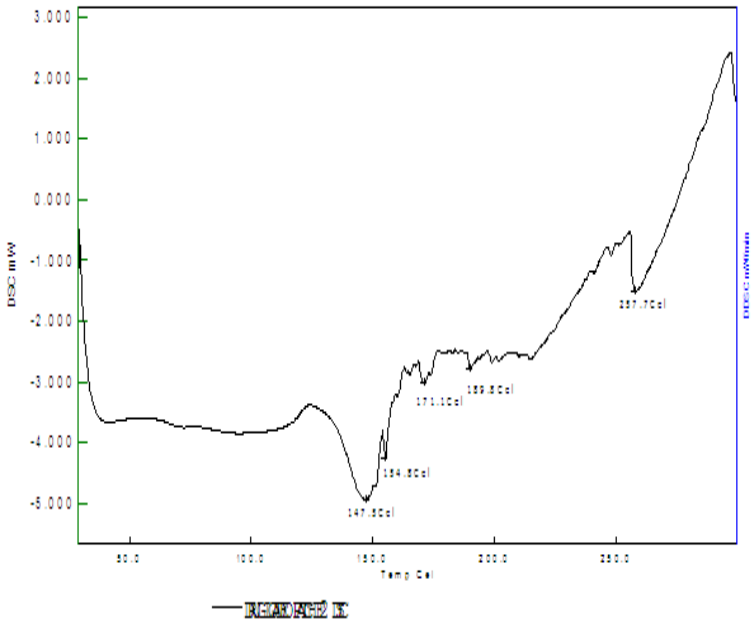

FIG 9: DSC curve of pure drug loaded patch F2

:	DSC	Temperature Program:						Comment:	
lame:	DRUG LOADED PATCH F4		Cel	Cel	Cel/min	min	s	Operator: BVCOP	
ement Date:	9/19/2013	1*	30	305	10	0	0.5	Gas1: N2	
: Name:	DRUG LOADED PATCH F4							Pan: Al	
: Weight:	10.000 mg								
nce Name:	ALUMINA								
nce Weight:	10.000 mg								

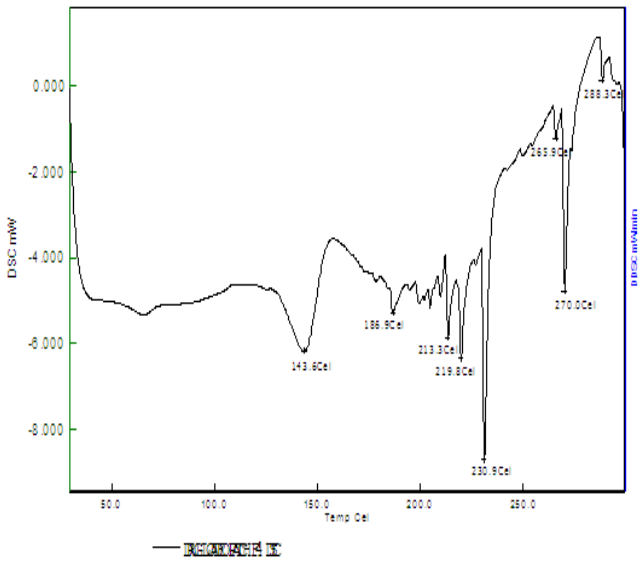

FIG 10: DSC curve of pure drug loaded patch F4

	DSC	Temperature Program:						Comment:	
me:	DRUG LOADED PATCH F6		Cel	Cel	Cel/min	min	s	Operator: BVCOP	
ment Date:	9/19/2013	1*	30	305	10	0	0.5	Gas1: N2	
Name:	DRUG LOADED PATCH F6							Pan: Al	
Weight:	10.000 mg								
ce Name:	ALUMINA								
ce Weight:	10.000 mg								

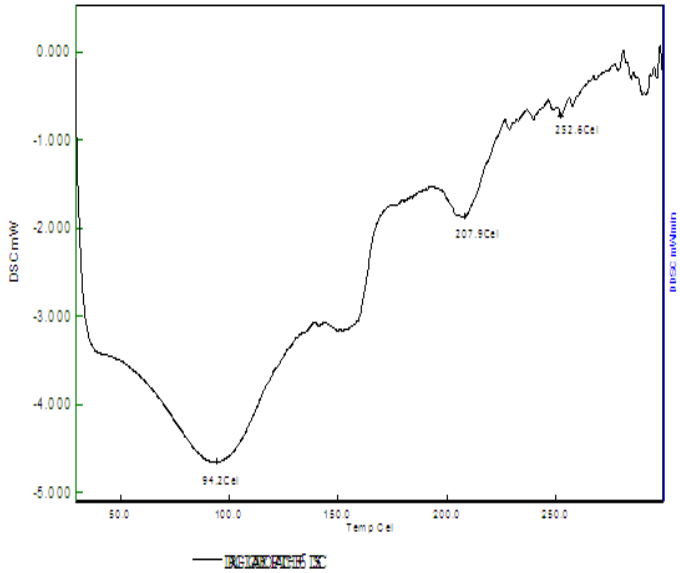

FIG 11: DSC curve of pure drug loaded patch F6

```
                DSC                          Temperature Program:                    Comment:
ıe:             DRUG LOADED PATCH F7                Cel  Cel  Cel/min  min    s   Operator: BVCOP
ıent Date:      9/19/2013                    1*      30  305       10    0  0.5   Gas1: N2
lame:           DRUG LOADED PATCH F7                                               Pan: Al
leight:         10.000 mg
ıe Name:        ALUMINA
ıe Weight:      10.000 mg
```

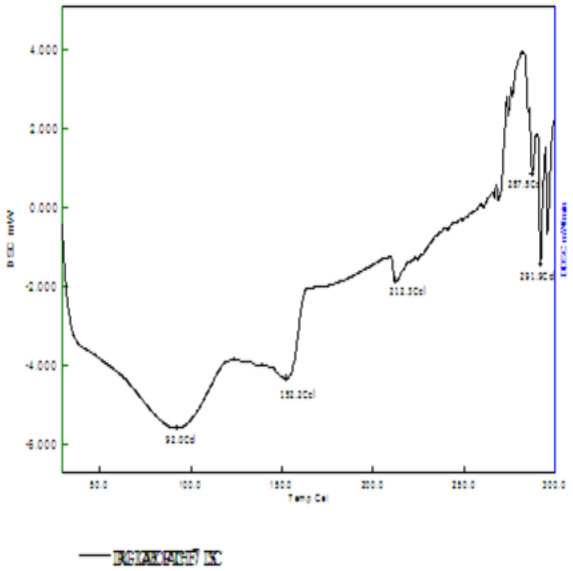

FIG 12: DSC curve of pure drug loaded patch F7

Data obtained from water vapour transmission studies for rate controlling membranes
Table no.6:

RCM	Amounted of water (gm) transmitted through RCM (Time in hrs)							WVT Rate constant (gm.cm/cm^2.12 hrs.)
	0	**2**	**4**	**6**	**8**	**10**	**12**	
F1	0	0.0267	0.0433	0.06	0.0765	0.09	0.0988	**0.00099979**
F2	0	0.0253	0.0404	0.0503	0.0586	0.0657	0.0733	**0.00059946**
F3	0	0.0219	0.038	0.0532	0.0691	0.0832	0.0911	**0.00074026**
F4	0	0.0186	0.0317	0.044	0.0523	0.0594	0.0673	**0.00056744**
F5	0	0.0178	0.0349	0.0532	0.0698	0.0812	0.0921	**0.00075241**
F6	0	0.013	0.0301	0.0457	0.0587	0.0721	0.0812	**0.000922324**
F7	0	0.01	0.024	0.0379	0.052	0.0646	0.0739	**0.000942717**
F8	0	0.0085	0.0197	0.0316	0.0457	0.0557	0.065	**0.000820664**

Tensile strength of Transdermal patches F1 to F8:
Table no.7.

Sl.no	Formulation code	Tensile strength (kg)	Extention value (mm)
1	**F1**	0.1697	2.229
2	**F2**	0.1227	2.0
4	**F3**	0.1224	2.2
5	**F4**	0.2641	1.6
6	**F5**	0.5017	1.5
7	**F6**	0.5648	1.4
8	**F7**	0.5833	1.36
9	**F8**	0.8249	1.36

% Swelling Index: Increase in weight of F1, F2, F3, F4, F5, F6, F7, F8

Table.no. 8

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8
Initial Weight(mg)	48	36	28	44	34	58	57	51
30 min	6.25	8.33	7.14	4.54	5.88	5.17	1.75	3.92
60 min	12.50	16.66	14.28	9.09	11.76	8.62	5.26	7.84
90 min	18.75	25	21.42	15.90	17.64	10.34	8.77	13.72
120 min	25	33.33	28.57	20.45	23.52	13.79	12.28	17.64
150 min	33.33	36.11	39.28	25	32.35	18.96	14.03	21.56
180 min	43.75	44.44	46.42	31.81	38.23	22.41	17.54	27.45
210 min	54.16	52.77	57.14	36.36	47.05	29.31	21.05	31.37
240 min	60.41	58.33	71.42	43.18	52.94	27.58	24.56	35.29
270 min	68.75	72.22	82.14	50	58.82	31.03	29.82	41.17
300 min	79.16	77.77	89.28	56.81	67.64	34.48	33.33	47.05
330 min	85.41	86.11	96.42	61.36	73.53	39.65	36.84	54.90
360 min	95.83	91.66	107.14	65.9	79.41	43.10	40.35	56.86

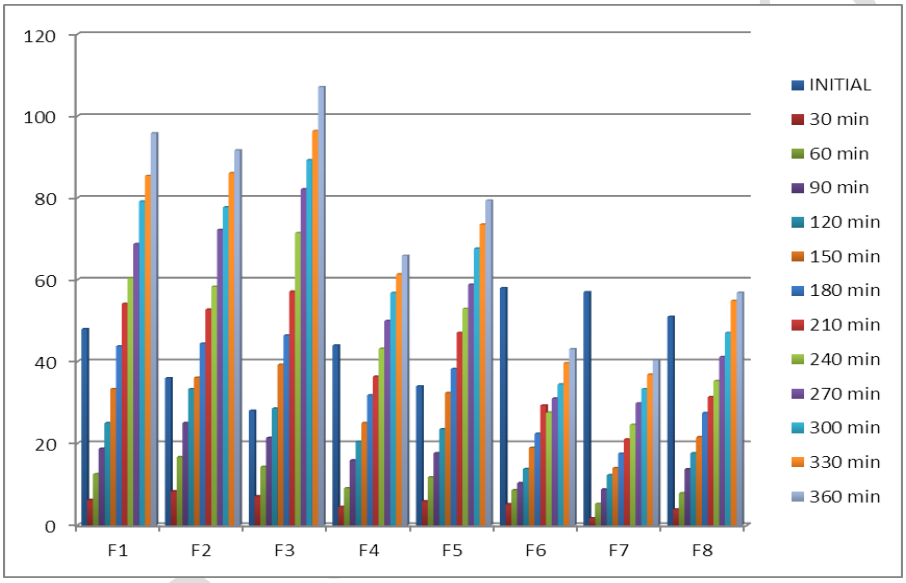

Fig.13: % Swelling index of increase in weight

TABLE 9: In vitro drug release of glibenclamide from F1 and F2 formulations through rat abdominal skin

Time(hr)	Log time	Square roots of Time	F1		F2	
		0	Absorbance	% drug release	Absorbance	% drug release
0	0	0.707	0	0	0	0
0.5	-0.301	1	0.077	12.29	0.061	09.74
1	0	1.224	0.091	14.53	0.082	13.09
1.5	0.176	1.414	0.106	16.92	0.101	16.12
2	0.301	1.732	0.124	19.80	0.121	19.32
3	0.477	2	0.151	24.11	0.142	22.67
4	0.602	2.236	0.182	29.06	0.176	28.10
5	0.698	2.449	0.223	35.61	0.216	34.50
6	0.778	2.645	0.256	40.88	0.253	40.40
7	0.845	2.828	0.294	46.95	0.274	43.75
8	0.903	3	0.361	57.65	0.339	54.13
9	0.954	3.162	0.421	67.23	0.391	62.44
10	1	3.464	0.478	76.33	0.432	68.99
12	1.079		0.516	82.40	0.494	78.79

TABLE 10: In vitro drug release of glibenclamide from F3 and F4 formulations through rat abdominal skin

Time (hr)	Log time	Square roots of Time	F3		F4	
			Absorbance	% drug release	Absorbance	% drug release
0	0	0	0	0	0	0
0.5	-0.301	0.707	0.069	11.01	0.066	10.54
1	0	1	0.086	13.73	0.085	13.57
1.5	0.176	1.224	0.112	17.88	0.107	17.08
2	0.301	1.414	0.132	21.08	0.130	20.76
3	0.477	1.732	0.164	26.19	0.154	24.60
4	0.602	2	0.197	31.46	0.181	28.90
5	0.698	2.236	0.241	38.48	0.231	36.89
6	0.778	2.449	0.272	43.43	0.264	42.16
7	0.845	2.645	0.323	51.58	0.303	48.38
8	0.903	2.828	0.364	58.13	0.343	54.77
9	0.954	3	0.418	66.75	0.384	61.32
10	1	3.162	0.468	74.73	0.441	70.72
12	1.079	3.464	0.521	83.20	0.478	76.33

TABLE 11: In vitro drug release of glibenclamide from F5 and F6 formulations through rat abdominal skin

Time(hr)	Log time	Square roots of Time	F5		F6	
		0	Absorbance	% drug release	Absorbance	% drug release
0	0	0.707	0	0	0	0
0.5	-0.301	1	0.059	9.42	0.048	7.66
1	0	1.224	0.077	12.29	0.069	11.01
1.5	0.176	1.414	0.101	16.12	0.089	14.21
2	0.301	1.732	0.131	20.92	0.116	18.52
3	0.477	2	0.156	24.91	0.138	22.03
4	0.602	2.236	0.183	29.22	0.172	27.46
5	0.698	2.449	0.214	34.17	0.208	33.21
6	0.778	2.645	0.242	38.64	0.239	38.16
7	0.845	2.828	0.276	44.07	0.286	45.67
8	0.903	3	0.297	47.43	0.314	50.14
9	0.954	3.162	0.323	51.58	0.354	56.53
10	1	3.464	0.367	58.60	0.379	60.52
12	1.079		0.398	63.55	0.419	66.91

TABLE 12: In vitro drug release of glibenclamide from F7 and F8 formulations through rat abdominal skin

Time(hr)	Log time	Square roots of Time	F7		F8	
			Absorbance	% drug release	Absorbance	% drug release
0	0	0	0	0	0	0
0.5	-0.301	0.707	0.056	08.94	0.065	10.38
1	0	1	0.071	11.33	0.088	14.05
1.5	0.176	1.224	0.091	14.53	0.109	17.40
2	0.301	1.414	0.112	17.88	0.141	22.51
3	0.477	1.732	0.141	22.51	0.181	28.90
4	0.602	2	0.167	26.66	0.221	35.29
5	0.698	2.236	0.211	33.70	0.242	38.64
6	0.778	2.449	0.228	36.41	0.271	43.27

7	0.845	2.645	0.264	42.16	0.308	49.18
8	0.903	2.828	0.301	48.06	0.346	55.25
9	0.954	3	0.337	53.81	0.397	63.39
10	1	3.162	0.361	57.65	0.416	66.43
12	1.079	3.464	0.379	60.52	0.448	71.54

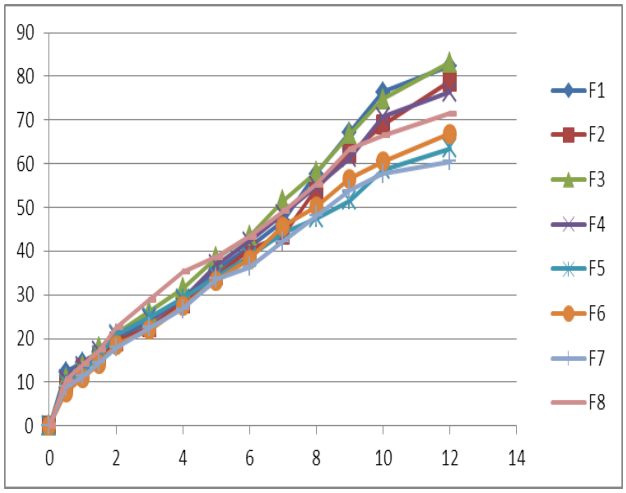

FIGURE 14: Glibenclamide permeation profiles of transdermal system through rat skin

TABLE 13: Flux (Jss) and permeability coefficients (pm) for transdermal system

Formulation	Passive permeation	
	Jss **(mg/cm^2/hr)**	***Pm*** **(mg/hour.cm)**
F1	0.149055	0.029811
F2	0.159577	0.031915
F3	0.149730	0.029946
F4	0.161809	0.032361
F5	0.196093	0.039218
F6	0.179760	0.035952
F7	0.195274	0.039054
F8	0.169012	0.033802

Data from the primary skin irritation test for prepared formulations

TABLE 14.

Formulations	Erythema	Edema
Control patch	+++	--
F1	+	--
F2	+	--
F4	+	--
F5	+	--

Scores: --: Nil, +: Mild, ++: Severe, +++: Very severe

DISCUSSION

Calibration curves of glibenclamide in 0.2M NaOH and phosphate buffer (Ph 7.4) solutions were constructed at λmax 229 nm with a UV-Visable spectrophotometer. Beer's law obeyed to construt the calibration curve in the concentration range of 1-5 µg/ml. Analyses were done in triplicate.

The FTIR spectra of pure drug has show characteristic peak of 3367, 3315, 2926, 1714, 1618, 1516, 1157 cm^{-1} due to –OH,-NH, -CH, -C=O function group. The similar peak were also noticed in the spectra of drug polymers, identify the stability of drug.

The DSC thermograph range of pure drug has shown and sharp endothermic peak of 175^{0}c due to its melting point, but this peak is not seen in the other thermograph of due to loaded formulations. This indicates that the drug has got uniformity dispersed in an amorphous from in the formulations.

In the present study, transdermal paches of glibenclamide were formulated using the polymer matrix of Eudragit, ethyl cellulose and effect of HPMC as rate-controlling polymer was studied. The prepared patches were characterized for physicochemical properties, in vitro release, invitro permeation profile excised hairless rat abdominal skin, and skin irritationstudies in rabbits.

The physicochemical properties of glibenclamide transdermal patchespresented in Table 3 & 4.

All the patches had uniform thickness. The thicknes results are given in Table 4. The result indicated that there was no much difference in the thickness within the formulations. The order of the thickness of film is F7>F8>F6>F1>F4>F2>F5>F3. Perusal to table 4 indicates, addition of DBP in the formulation F1 to F8 increased the thickness of film. DBP decreases interfacial tension and increases wetting of polymer by solvent. This result in more swelling during evoparation. Even after complete drying, the swollen polymer gave thicker film.

Drug loaded patch (1* 1 cm^2) were tested for uniformity of weight and the result of weight are given in Table 6. The order of weight of film is F7>F6>F8>F4>F1>F2>F5>F3. This is in agreement with the uniform of the thickness. Perusual to Table 1 indicate that patch F7 exhibited highest weight.

The swelling of the drug loaded patches of size 2 * 2 cm^2 was studided up to 30 min in case of change in weight and 60 min in case of change in area. The swelling of the patches were observed in phosphate buffer solution (pH 7.4). The order of patches for their increase weight due to swelling is F7<F6<F8<F4<F5<F2<F1<F3. Further, it should be verified with increase in area due to swelling.

The tensile strength of formulated films was measured using bottom loading single pan balance. The order of

tensile strength of film is F3<F2<F1<F4<F5<F6<F7<F8. The soluble polymer develops crosslinking better than insoluble polymer. More the solubility of the polymer higher will be the tensile strength and extensive value between 1 to 2.2 as show in table 6.

In order to evaluate the flexibility, the films were subjected to tensile strength, extensive value and folding endurance studies. The tensile strength of the patches was found vary with the nature of the adhesive and also enhancers. The values of tensile strength of the patches was very identical to the innovator product. The value of folding endurance was found to be greater than 250 in all batches. This revealed that the prepared patches were having capability to withstand the mechanical pressure along with good flexibility. Drug content in all formulation was observed within the range of 82 to 94, which was found to be satisfactory.

The patch formulated F1 showed maximum water vapour transmission rate of 0.00099979.

In-vitro release studies for all the prepared patches were carried out for 12 hours. % cumulative drug release after 12 hours was taken and compared for all the patches. F1 and F3 exhibited maximum drug release at the end of 12th hour. Results are as shown in the table. Fig 8. show the release profiles of Glibenclamide from transdermal patches. Formulation F1 exhibited greatest (82.40% respectively) percentage of drug release values after 12 hrs, which are significantly different compared to the lowest values observed with the formulation F7 (60.52% respectively). However with a very nominal decrease in formulation F7. The addition of hydrophilic component to an insoluble film former tends to enhance the release rates.

No erythema was observed from a primary skin irritation test carried out on rabbits after the application of transdermal films. The absence of erythema indicated that these polymeric patches of glibenclamide were compatible with skin and hence can be used for the transdermal application. Patch does not cause any noticeable irritation on the skin throughout the study.

The film were subjected for stability studies for one month and observed for change in appearance and flexibility at a temperature of 40^0C. There were no physical change in appearance, flexibility. The percentage of degradation with respect to drug content of the patch was observed was low (2-3%). Hence, the formulations were stable.

Result from present study concluded that Glibenclamide with Eudragit, ethyl cellulose, HPMC with incorporation of DBP produced smooth and flexible film. The release rate of drug through films and permeation across skin increased when the concentration of hydrophilic polymer was increased. In view of the overall result reported in the present study, it is proposed that Glibenclamide used in the formulation of matrix type transdermal drug delivery system to prolong the drug release.

CONCLUSION

The transdermal drug delivery system have been developed for controlled transport of drug tr effective drug action. For this purpose, the fibraction of transdermal patch requires a suitable rate controlling membrane.

In present study, attempts were made to prepare and evaluate the matrix type transdermal drug delivery contaialning for glibenclamide. Glibenclamide transdermal films made up of Eudragit RL100, Ethyl cellulose and HPMC were used as polymerrate controlling membrane and DBP were used as plastisizer. The transdermal patch evaluated for their, appearance, weight uniformity, thickness uniformity, Fourier transform infrared, differential scanning colorimetry, tensile strength, swelling index, water vapour transmission, skin irritation and stability studies. All the patches were, thin and flexible; uniformity and thickness were observed with the low SD values. The rate controlling membrane were permeable to water vapors depending upon the thickness of membrane. The transdermal were tested for the skin irritation on rabbits and no significant irritation was observed. In-vitro drug permeation through rat abdominal skin was performed using Keshary-Chain diffusion cells. The drug released study followed by Flux and permeability coefficient.

The FTIR spectra of pure drug has show characteristic peak of 3367, 3315, 2926, 1714, 1618, 1516, 1157 cm^{-1} due to –OH,-NH, -CH, -C=O function group. The similar peak were also noticed in the spectra of drug polymers, identify the stability of drug.

The DSC thermograph range of pure drug has shown and sharp endothermic peak of 175^0c due to its melting point, but this peak is not seen in the other thermograph of due to loaded formulations. This indicates that the drug has got uniformity dispersed in an amorphous from in the formulations.

From the above experimentel results can be reasonably concluded that:

- The formulated TDD paches F1 to F8 showed good physical properties.
- 30% w/w of DBP were suitable plastisizer for F1 to F8 formulations respectively.
- All the optimized paches formulated were stable at room temperature.
- FTIR and DSC studies indicated comparibility between the drug and the excipients employed in the fabrication of TDDS, which was further confirmed by accelerated stability studies as per ICH guidelines.
- Formulated paches did not show any skin irritation reaction.

- The properties of adhesion to skin and loss painful peel-off can improve by additional plasticizer, DBP.
- Matrix type transdermal therapeutic systems of Glibenclamide could be prepared with the required flux having suitable mechanical properties.
- Further work is recommended in support of its efficacy claims by long term pharmacokinetic and pharmacodynamic studies on human beings.

REFERENCE

1. Patel K.A., Patel H.K., Patel V.A. "Formulation and Characterization of drug in adhesive transdermal patches of diclofenal acid". Ind. J. Pharm. Sci., 2012; 4: 1.
2. Narasimha Rao R., Askulla S., Bhavya B., Prasoona Ch., Koppu P. "Design and Evaluation of Glipizide Transdermal Patches". Int. J. Pharm. Biomedical Sci., 2011; 2: 4.
3. Sonjoy M., Thimmasetty J., Ratan G.N., Kilarimath B.H. "Formulation and Evaluation of carvedilol transdermal patches". Int. Res. J. Pharm., 2011; 2(1): 237-248.
4. Narendra P., Manvi P., Bhaskar V.H., Patel K.R. "Development of Transdermal drug delivery system of a model antidiabetic agent". J. Pharm. Sci. Bioscientific Res., 2011; 1(1): 59-64.
5. Sharma A. "Transdermal approach of antidiabetic drug Glibenclamide". Int. J. Pharm. Res. Dev., 2012; 3(11): 25-32.
6. Mautalik S., Udupa N. "Design and Evaluation of Glipizide Transdermal Patches". J. Pharm. Pharmceut. Sci., 2012; 8(1): 26-38.
7. Pandit V, Khanum A, Bhaskaran S, Banu V. Formulation and evaluation of transdermal films for treatment of overactive bladder. Int. J. of Pharm Tech Res., 2009; 1(3): 799-804.