Preparation and Characterization of Extended Release Transdermal Patches of Glimepiride

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ABSTRACT

Objective: The main objective is to Preparation of suitable transdrmal patches of Glimepiride (anti-diabetic drug) using different ratio of polymers (Hydroxy Propyl Methyl Cellulose 50cps and Poly Vinyl Pyrrolidone K-30) as per the requirement of the patient used (patient compliance) and for better drug release than the other type of formulation. In these formulations Di-N-Butyl Phthalate was incorporated as plasticizer and Tween-80 was used as a permeation enhancer. Franze diffusion cell was used for the in-vitro skin permeation studies using phosphate buffer pH 7.4.

Method: Matrix type of transdermal patches were prepared by solvent evaporation technique using magnetic stirrer.

Results: Beer's law was followed Over a concentration range of 2-12 μg/ml in phosphate buffer pH 7.4. The linear regression equation of pure drug was found to be $Y=0.490x=0.211$ and R^2 value was 0.999. Better drug release of formulation F5 than the other formulation follows zero order release kinetics and R^2 value was 0.998. In skin irritation study there is no rashes found in rat skin.

Conclusion: The FTIR AND DSC studies of drug polymer interaction suggested there is no interaction found between drug and polymers. Formulation F5 showed negligible change in % of drug content and permeation profile for a period of 90 days studies.

Keywords: Glimepiride, Tween-80, Di-N-Butyl Phthalate, Franze diffusion cell

I.   INTRODUCTION

Transdermal drug delivery is one of the most capable drug application technique used when for potent drug. In recent years, there has been renewed interest in the development of transdermal drug delivery systems for existing drug molecules. The development of a transdermal delivery system for existing drug molecules improves not only the drug's performance in terms of safety and efficacy, but also therapeutic benefit and patient compliance.[1]

Glimepiride is a third-generation sulfonylurea used to treat diabetes. Patients with type 2 diabetes are frequently prescribed this drug. However, due to its poor solubility and, poor bioavailability Glimepiride is choice of drug for formulation of transdermal patches. A transdermal delivery approach for glimepiride should be tried for convenient, safe, and successful anti-diabetic activities. For preparation of transdermal patches we used to polymers namely HPMC and PVP in different concentrations in nine formulations (Table No.1). Patches were evaluated for checking its physical properties and in-vitro dissolution characteristics where the formulation F5 shown better results.[2]

II.   MATERIALS AND METHOD

Materials: Pure Glimepiride was collected as gift sample from Dey's Medical Private Limited, Kolkata. Potassium di-hydrogen orthophosphate, Di-Sodium hydrogen phosphate, Methanol, NaCl , Di-n Butyl phthalate ,PVP K30,HPMC 50 cps ,Tween-80 were purchased from local market. All reagents used in this study were of analytical grade.

Method: Extended release of transdermal patches containing glimepiride were prepared by solvent evaporation technique, using different ratio of HPMC (50cps) and PVP K30. Two polymers were mixed in the appropriate ratio and dissolved in distilled water. Methanol was used to dissolve glimepiride, which was then added to the polymeric solution. When uniform mixture was achieved, Di-n Butyl phthalate was added in the above solution as plasticizer. Tween-80 was also incorporated as permeation enhancer. The whole solution continuously stirrer with the help of magnetic stirrer to form homogeneous mixture for 30 mins. The above solution was poured into the Petri plate and covered with funnel and allowed to evaporate the solvent for 24 hrs at room temperature for solidification. The entire sheet was

cut into small patches with an area of 3.14 cm^2, corresponding to a diameter of 2 cm. Each sheet yielded approximately nine patches.[3,4]

Patches were packed properly with aluminium foil and kept in a dessicator for evaluation.

Fig. 1: Transdermal patches

Formulation Table

Table 1: Formulation Table

Batches	Drug (mg)	PVP K30 (mg)	HPMC(50cps) (mg)	Methanol (ml)	Sterile water (ml)	Di-N-Butylphthalate (ml)	Tween-80 (ml)
F1	50	600	200	2	10	0.3	q.s
F2	50	550	250	2	10	0.3	q.s
F3	50	500	300	2	10	0.3	q.s
F4	50	450	350	2	10	0.3	q.s
F5	50	400	400	2	10	0.3	q.s
F6	50	350	450	2	10	0.3	q.s
F7	50	300	500	2	10	0.3	q.s
F8	50	250	550	2	10	0.3	q.s
F9	50	200	600	2	10	0.3	q.s

PRELIMINARY STUDY

A. **Determination of λmax:** Glimepiride 10mg was precisely weighed and first dissolved in 20 ml methanol solutions. These solutions were then diluted up to 100 ml phosphate buffer pH-7.4 solution. The UV spectrum (Shimadzu-1700, Japan) was captured at wavelengths ranging from 200 to 400nm using Shimadzu 1700 spectrophotometer **(Fig. 2)**.

B. **Preparation of calibration curve for Glimepiride:** The phosphate buffer pH 7.4 media was used to concentrate the sample. It was spectrophotometrically analyzed by measuring absorbance at 221.2 nm wave length. Table no. 1 displays the absorbance values. The calibration curves in figure no have a slope of 0.0717 and a regression value of 0.9999. The curve was found to be linear in the range of 2- 12 µg/ml at the concentration of 100 g/ml in the drug solution. serial dilution 2, 4, 6, 8, 10, 12 µg/ml **(Table 2 & Fig. 3)**.[5]

C. **Fourier Transform Infrared Spectral studies of Glimepiride:** A FTIR spectrophotometer (Averinbiotech pvt. Ltd, Hyderabad) was used to determine the spectra of Glimepiride. The Agilent Cary 630nm, FTIR Spectrophotometer was used to record the FT-IR spectra of Glimepiride. The sample was placed in a sample holder, and scanning was done between 4000 cm^{-1} and 400 cm^{-1} **(Fig. 4)**.

D. **Drug excipients compatibility studies:** Before formulation, it is critical to test the compatibility of the drug and polymers under experimental conditions. It is necessary to ensure that the drug does not react with the polymer and excipients during the manufacturing process, and that it does not affect the product's shelf life or cause any other unwanted effects on the formulation. Infrared spectrums were determined using a physical mixture of drug and polymers **(Fig. 5)**.

E. **Differential scanning calorimetry (DSC) studies for Glimepiride:** DSC is a thermo analytical technique that measures the amount of heat required to raise the temperature of a sample and a reference as a function of temperature. Throughout the experiment, both the sample and the reference are kept at nearly the same temperature. In general, the temperature programme for a DSC analysis is designed so that the sample holder temperature increases linearly with time. The reference sample should have a well-defined heat capacity across the temperature range being scanned **(Fig. 6)**.[6]

Evaluations Of Transdermal Patches

1. **Thickness:** Patch thickness was measured three times of different site of patch with a digital micrometer of screw gauge, and the mean value was calculated **(Table 3)**.[7]

2. **Weight Uniformity Test:** Weight uniformity of dried and cut patches was examined on a digital weight balance, and weight variation was tested by randomly picking three patches from each formulation. The average weight of three patches of 1.5 cm^2 from each formulation provided information on weight variation between formulations **(Table 3)**.[8]

3. **Folding endurance:** The folding endurance of patches was tested by folding a 2×2 cm polymeric film repeatedly at the same point until it broke. The 2×2 cm of film was taken from both the centre and the edge of the patch. The experiment was carried out on three randomly selected patches from each formulation. The average and standard deviation were calculated **(Table 4)**.[9]

4. **Percentage moisture content:** The produced films were weighed separately and maintained at room temperature for 24 hours in a desiccator containing fused calcium chloride. After 24 hours, the films were reweighed and the moisture content was calculated **(Table 5)** using the formula below.

Percentage moisture content
$$= \text{(Initial weight-Final weight)/Final weight} \times 100$$

5. **Percentage moisture uptake:** For each formulation, the percentage moisture uptake was calculated. Each patch was cut into a 1×1 cm transdermal film. A digital weighing balance was used to weigh each film individually. These films were then placed on labelled Petri dishes and kept at 25 ° C for 84 percent relative humidity in a desiccator containing 200 ml saturated potassium chloride solution (RH). The transdermal films were continuously weighed for 5 days of storage or until they reached a steady weight. The following formula was used **(Table 5)** to determine the % moisture uptake:[10]

Percentage moisture uptake
$$= \text{(Final weight-Initial weight)/Initial weight} \times 100$$

6. **Drug content:** 2 cm × 2 cm patch sample was cut and weighed precisely. Each sample was

dissolved in 100 ml of phosphate buffer solution and stirred with a magnetic stirrer for 24 hours. A UV-VIS spectrophotometer set to 228 nm was used to examine the solution. Glimepiride's total content has been calculated. The result was the mean ± standard deviation of the three measurements **(Table 6).**

7. Skin irritation study: Rats (average weight 1.0-1.5 kg) can be used to test skin irritation and sensitization. The rat's dorsal surface (50 cm^2) should be washed, and hair should be removed from the clean dorsal surface by shaving. The surface should then be cleaned with rectified spirit, and a representative formulation applied to the skin. After 24 hours, the patch is removed, and the skin is graded into five categories based on the degree of the skin injury **(Fig. 8).**

8. In-vitro drug release study: The Franz diffusion cell consists of an upper donor compartment and a lower receptor compartment surrounded by a water jacket to keep the receptor phase temperature at 32 ± 1^0 C. Stirring speed was used 600rpm to keep the solution uniform movement in the receptor phase with a tiny Teflon coated magnetic bead. The receptor compartment's volume was kept constant at 60ml. The receptor compartment was equipped with a sampling port on one side to withdraw samples at predetermined time intervals for drug content estimation using a UV spectrophotometer. Phosphate buffered saline (PBS) pH 7.4 was used as the receptor medium **(Fig. 9.)[11]**

9. Skin permeation study: The dorsal skin of rats was removed. A sharp scissors was used to remove the hair and underlying tissues. The skin was properly cleansed using distilled water and regular saline. Before use, it was soaked overnight in regular saline and rinsed numerous times. After that, the skin was sliced to size and put between the compartments of the diffusion cell, with the stratum corneum facing the donor compartment. It was kept on the receptor fluid overnight to stabilize and optimize it. The matrix formulation for testing was cut into 1cm patches (n=3) and applied to the optimal skin. The occlusive backing was then coated with aluminium foil. With the use of springs, the donor compartment was clamped over it, ensuring that there were no air bubbles in the receptor chamber. 1 ml samples were taken at specified intervals up to 12 hours. To maintain a constant volume, new receptor fluid was supplied to the receiver compartment. The filtered samples were then examined at 221.2 nm with a UV double beam spectrophotometer (Schimadzu-1700, Japan). From 2 to 12 g/ml, linearity was demonstrated (R^2 > 0.999) **(Table 7).[12]**

10. Scanning electron microscope of the patch (SEM): A scanning electron microscope (Averinbiotech pvt. Ltd, Hyderabad) was used to examine the exterior morphology of the transdermal patches. The stub samples were delicately coated with gold and examined under a microscope **(Fig. 10).**

11. Stability studies:
Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40 ± 0.5^0c and 75 ± 5 % RH for 6 months. The samples are withdrawn at 0,30,60,90 days and analyze suitably for the drug content (Table 9).[13]

III. RESULTS AND DISCUSSION

1. Preliminary studies:
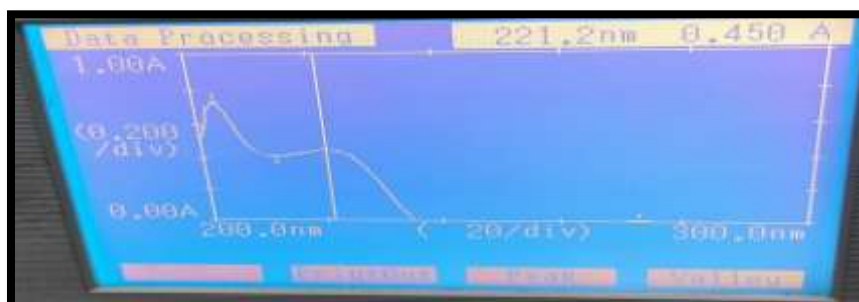i. **Determination of λ max:**

Fig. 2: λ max of glimepiride

ii.   **Standard calibration curve for Glimepiride:**
Table 2 : Raw data of glimepiride for calibration curve

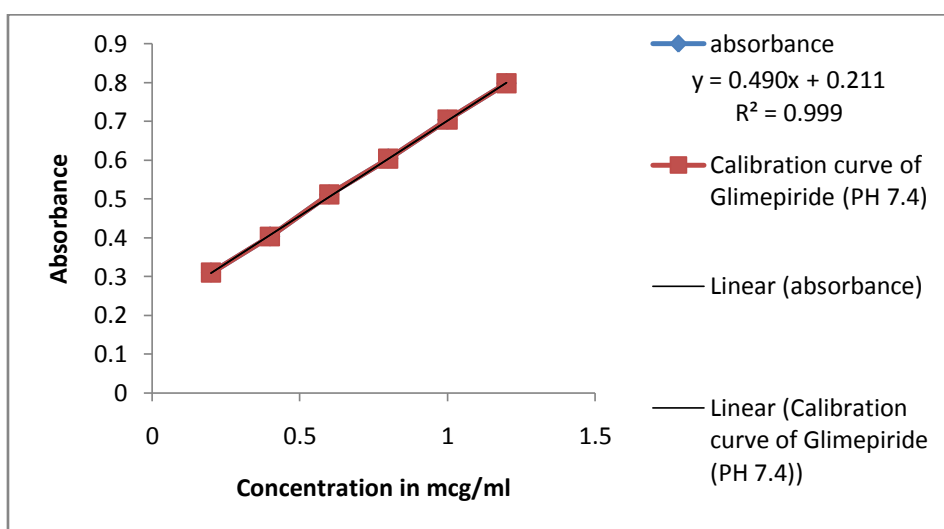| Serial No	Concentration (mcg/ml)	Absorbance
1	0.2	0.310
2	0.4	0.403
3	0.6	0.511
4	0.8	0.604
5	1.0	0.704
6	1.2	0.798

y = 0.490x + 0.211
R² = 0.999

Fig. 3: Standard calibration curve

iii.   **Drug & excipients compatibility study:**
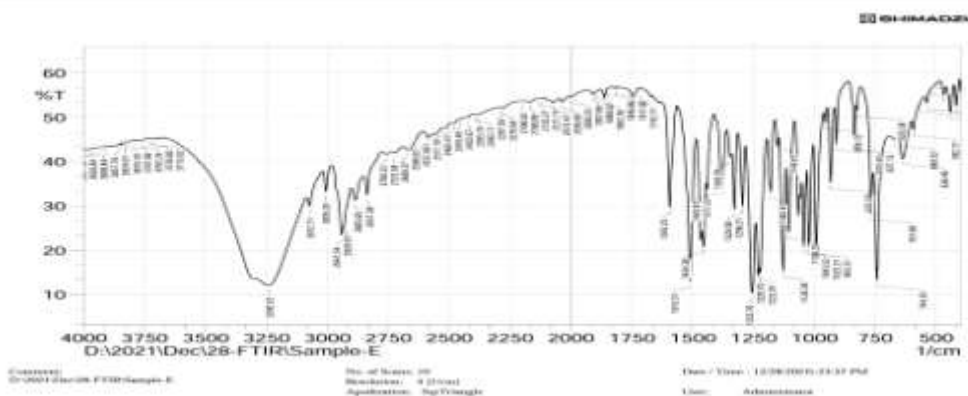 A.   **FTIR Spectra of Glimepiride**

Fig. 4: FTIR Spectra of pure drug (Glimepiride)

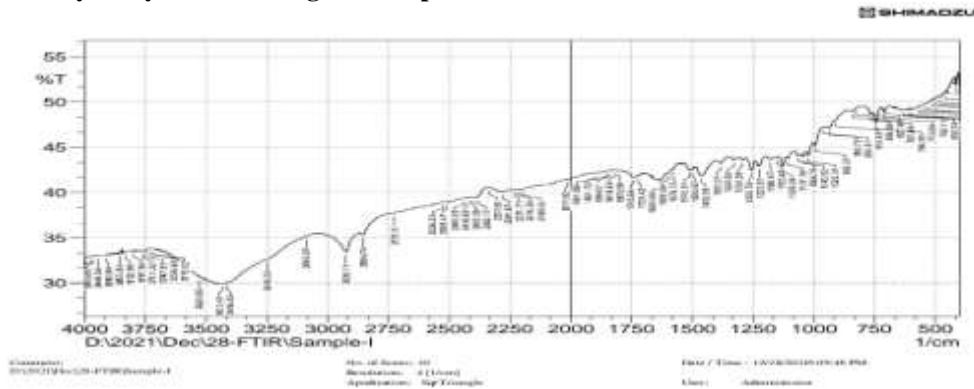**B. Compatibility study between drug and excipients**

Fig. 5: FTIR Spectra of drug with excipients

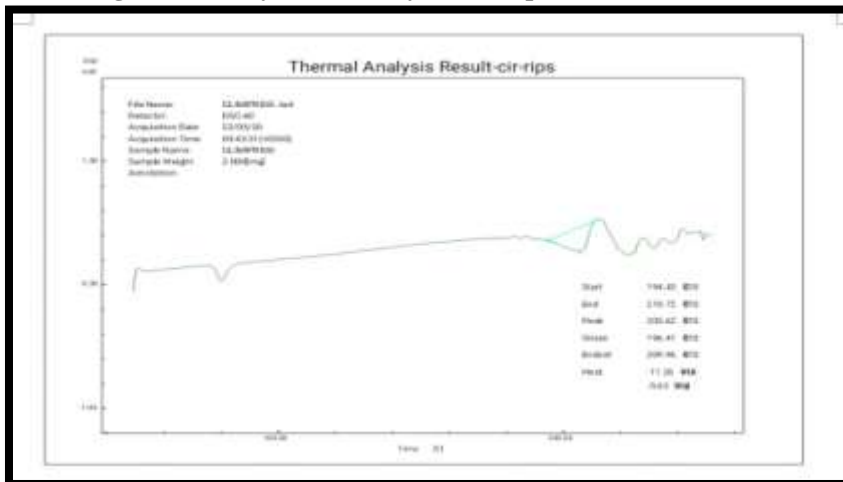**C. Differential Scanning Calorimetry (DSC) study of Glimepiride**

Fig. 6 : DSC Spectrum of Drug

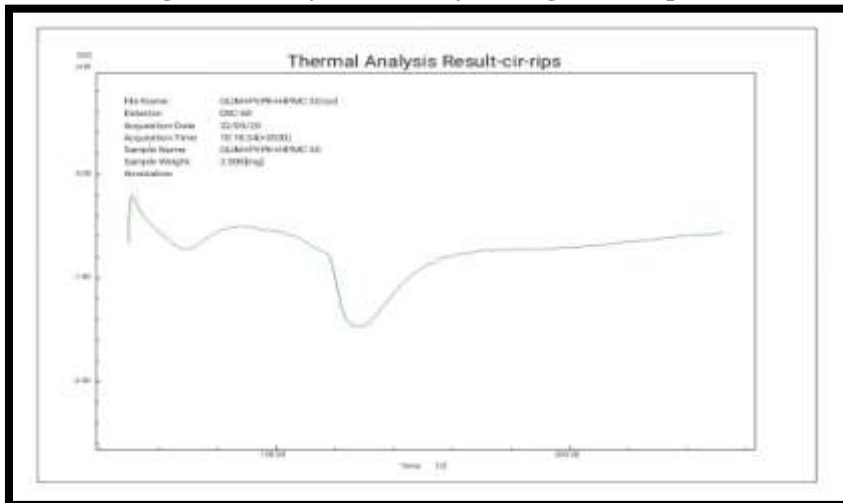**D. Differential Scanning Calorimetry (DSC) study of drug with excipients**

Fig.7: DSC Spectrum of Drug with Excipients

2. **Evaluation studies of transdermal patches:**
A. **Thickness and Weight Uniformity :**

Table 3: Thickness study & Weight uniformity study

SL NO	FORMULATION CODE	THICKNESS (mm)*	WEIGHT UNIFORMITY*
1	F1	0.65±0.032	1.09±0.011
2	F2	0.90±0.0121	1.07±0.04
3	F3	0.66±0.053	1.17±0.051
4	F4	0.78±0.013	1.13±0.08
5	F5	0.96±0.172	1.02±0.03
6	F6	0.68±0.078	1.11±0.09
7	F7	0.69±0.067	1.19±0.011
8	F8	0.81±0.019	1.16±0.021
9	F9	0.71±0.039	1.04±0.032

*Mean±SD (n=3)

B. **Folding endurance:**

Table 4: Folding endurance study

SL NO	FORMULATION CODE	CRUSHING FORCE
1	F1	4 times
2	F2	3 times
3	F3	3 times
4	F4	5 times
5	F5	4 times
6	F6	4 times
7	F7	6 times
8	F8	5 times
9	F9	5 times

C. **Percentage moisture content and Percentage moisture uptake:**

Table 5: % moisture content & % moisture uptake

SL NO	FORMULATION CODE	% MOISTURE CONTENT*	% MOISTURE UPTAKE*
1	F1	6.39±0.086	3.24±031
2	F2	1.84±0.104	1.19±0.11
3	F3	3.98±0.011	1.30±0.231
4	F4	5.09±0.09	2.64±0.49
5	F5	3.06±0.065	2.19±0.121
6	F6	1.09±0.081	1.35±0.066
7	F7	2.98±0.032	3.49±0.022
8	F8	5.07±0.091	3.45±0.043
9	F9	2.05±0.07	1.35±0.107

*Mean±SD (n=3)

D. **Drug content:**

Table 6: % of Drug content

SL NO	FORMULATION CODE	% OF DRUG CONTENT*
1	F1	93.23±0.623
2	F2	89.87±0.241
3	F3	95.93±0.042
4	F4	92.82±0.143
5	F5	98.41±0.078

6	F6	91.53±0.061
7	F7	87.72±0.015
8	F8	94.73±0.164
9	F9	96.62±0.241

*Mean±SD (n=3)

E.   Skin irritation study: From the skin irritation study on rat it had been found that there were no rashes arised.

Fig. 8: Skin irritation study on rat

F.   In-Vitro skin permeation studies:

Table 7: Zero order release kinetics data

TIME (Hours)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	7.36±0.41	8.04±0.51	12.13±0.74	5.73±0.22	10.09±0.03	6.52±0.09	9.41±0.21	11.62±0.69	8.52±0.41
2	14.18±0.72	11.29±0.03	15.04±0.32	8.10±0.50	15.73±0.62	10.61±0.84	13.76±0.03	14.84±0.43	12.95±0.07
3	19.70±0.14	15.35±0.79	18.73±0.93	12.09±0.08	19.24±0.74	13.92±0.59	16.84±0.06	18.93±0.03	15.63±0.82
4	25.85±0.75	20.14±0.05	23.62±0.09	16.43±0.39	25.41±0.31	18.06±0.03	20.07±0.72	23.28±0.76	19.22±0.03
5	30.51±0.61	24.91±0.84	27.56±0.68	21.77±0.81	31.88±0.09	22.67±0.82	23.55±0.89	28.02±0.04	24.64±0.49
6	35.04±0.49	29.82±0.66	32.08±0.52	27.51±0.63	37.30±0.47	27.59±0.19	28.09±0.61	35.29±0.53	29.91±0.86
7	43.91±0.03	35.15±0.71	36.81±0.70	33.98±0.71	42.98±0.79	32.08±0.27	31.38±0.12	40.73±0.11	33.09±0.22
8	51.05±0.81	40.01±0.60	41.23±0.01	39.36±0.01	50.61±0.99	37.11±0.53	36.44±0.74	46.44±0.86	38.64±0.94
9	55.13±0.47	46.39±0.05	44.51±0.81	45.32±0.49	56.45±0.11	42.85±0.01	41.94±0.01	53.70±0.09	42.09±0.08
10	60.92±0.39	51.22±0.34	48.20±0.33	49.03±0.07	60.70±0.57	47.79±0.81	45.08±0.42	58.18±0.35	47.68±0.47
11	64.77±0.01	55.09±0.49	53.85±0.29	54.23±0.55	66.91±0.01	53.97±0.42	51.01±0.99	63.39±0.01	53.44±0.26
12	68.41±	61.86±	58.09±	59.79±	71.24±	60.36±	57.72±	69.37±	59.87±

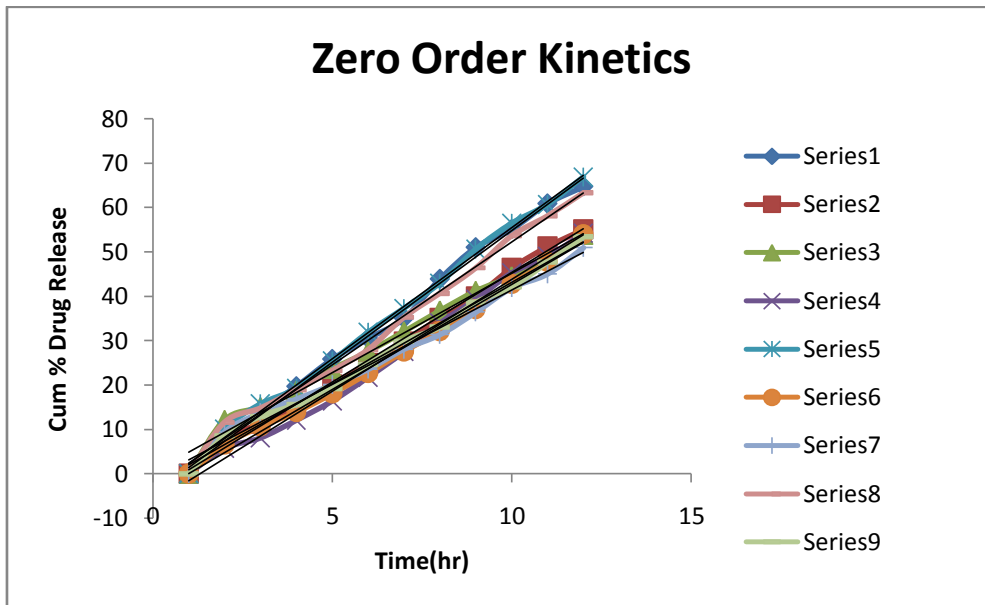| 0.52 | 0.01 | 0.17 | 0.93 | 0.52 | 0.83 | 0.26 | 0.04 | 0.42 |

Fig. 9 : Drug release profile of formulation F1-F9

Table 8 : Different release kinetics data of all transdermal patches formulation

FORMULATION	Zero order		First order		Higuchi's model		Korsmeyer-peppar model	
	R^2	Slope	R^2	Slope	R^2	Slope	R^2	Slope
F1	0.994	5.707	0.986	-0.043	0.980	26.15	0.991	0.908
F2	0.996	4.962	0.973	-0.034	0.959	22.47	0.982	0.862
F3	0.995	4.235	0.984	-0.029	0.968	19.26	0.972	0.667
F4	0.995	5.147	0.997	-0.034	0.956	23.29	0.981	1.018
F5	0.998	5.736	0.998	-0.045	0.993	26.12	0.996	0.821
F6	0.993	4.864	0.962	-0.032	0.948	21.94	0.987	0.912
F7	0.990	4.250	0.960	-0.028	0.943	19.15	0.973	0.730
F8	0.994	5.453	0.965	-0.041	0.953	24.64	0.964	0.772
F9	0.993	4.591	0.965	-0.030	0.951	20.7	0.979	0.798

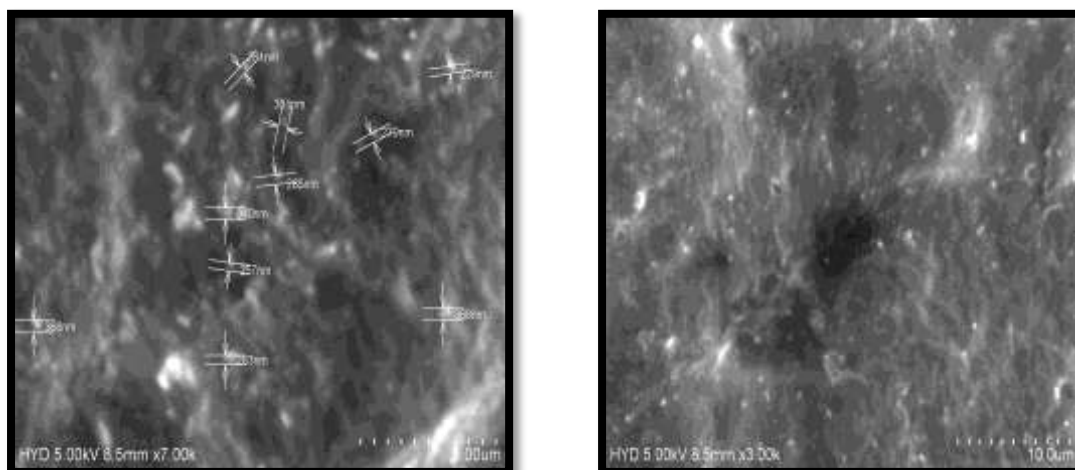**G.** **Scanning Electron Microscope study of patch:**

Fig. 10 : SEM analysis of Glimepiride matrix patch before and after permeation(F5)

H. Stability study

The result are given in the following table % drug content F5 during stability study.

Table 9 :

Time in Days	% Drug content	% moisture content
0	95.41±0.078 %	3.97±0.065
30	95.02±0.481	3.78±0.091
60	94.27±0.793	3.49±0.05
90	92±0.512	3.07±0.071

IV.   CONCLUSION

The procedure for making glimepiride transdermal patches disclosed in this study is simple. All formulations had good physicochemical features such as thickness and weight variation, release data, which demonstrated that the types of polymer and concentration of polymer impacted drug release from the patch formulation. The effect of penetration enhancers such as tween-80 on drug absorption in vitro has been studied. Glimepiride transdermal patches may provide transdermal delivery for extended periods in diabetic therapy, which can be moderately useful for the preparation of extended release matrix transdermal patch formulations.

The chosen formulation F5 met all of the pharmaceutical parameters of transdermal films and appears promising. Formulation F5 releases near about 71.24% drug that is better drug release than other type formulation. It could provide benefits such as extended drug release, reduced frequency of drug administration, improved bioavailability, and thus may help to improve patient compliance. Based on drug release behaviour using kinetic models such as zero order, first order, Higuchi's, Peppas model. Finally, F5 has been observed to exhibit Fickians release. This technology can also be applied to other anti-diabetic molecules in order to achieve better disease control.

V.   ACKNOWLEDGEMENT

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