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FORMULATION AND PREPARATION OF TRANSDERMAL PATCHES OF GLIMIPRIDE (PART -1)

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ABSTRACT: Transdermal drug delivery has been accepted as a potential non-invasive route of drug administration, with advantages of prolonged therapeutic action, less side effect, easy use, and improved patient compliance. Glimepiride is an anti-diabetic drug with a shorter half-life of ~ 5 h, low bioavailability, and extensive first-pass metabolism due to these limitations required to maintain the therapeutic level it has chosen as a transdermal drug delivery system. The present study was to formulate and evaluate the transdermal drug delivery system of Glimepiride using polymers such as tristearin, soya lecithin & Eudragit RS100 by solvent casting technique. Central composite design (CCD) was applied by using design-expert to optimize the composition of tristearin and soya lecithin for transdermal drug delivery. The prepared formulations were evaluated for different physicochemical characteristics like weight variation, folding endurance, flatness, pH of patches, % moisture content, % moisture uptake, % elongation, % drug content and % drug release.

Keywords: Transdermal patches, Transdermal drug delivery, Glimepiride, Solvent casting method

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INTRODUCTION: Recent advances in nano-particulate systems for improved drug delivery display a great potential for the administration of a wide variety of active pharmaceuticals. Nowadays, about 74% of drugs are taken orally and are found not to be as valuable as most wanted [1, 19]. The main challenge in transdermal drug delivery is to overcome the inherent barrier of the skin.

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There is evidence that the rate-limiting step in transdermal transport occurred at the stratum corneum. Many approaches have been used to enhance the penetration of drugs through the skin. Some of the transdermal delivery attempts resulted in showing success in delivering glucose responsive doses (approximately 20 - 50 mIU/mL) of insulin over short periods [2]. The role of these systems in the long-term treatment of diabetes, however, remains debatable.

Especially questionable are those methods involving physical or chemical disruption of the skin, which might cause chronic pathological changes. The transdermal route, in particular, is an attractive candidate for the steady and sustained

delivery of insulin into the blood. Although the stratum corneum poses a significant barrier for protein absorption, once the protein passes through this barrier, the transdermal route offers several unique advantages. Firstly, proteolytic degradation of the drug is low because the skin contains relatively few proteases. Secondly, painless, noninvasive, and patient-friendly application of patches offers good patient compliance. Thirdly, patches are also easy to remove in the event of hyperinsulinemia [3]. The use of drug carriers as a vehicle for transdermal delivery is a good strategy [4]. Drug carrier could modify the physiochemical properties of the encapsulated molecules and facilitate percutaneous delivery. Recently, they are some report about liposomes [5], microemulsions; polymeric nanoparticles loaded transdermal films [6].

SLN has been proven a better alternative carrier system than conventional systems. They produce prolonged release and protect the drug against chemical degradations. Compared to polymeric nanoparticles, they possess some distinctive effect apart from the lower cytotoxicity due to the absences of solvent and relatively low cost for excipients and large scale up production is possible by the simple process of homogenization [7].

Glimepiride, a third-generation sulfonylurea drug, is effective for the treatment of type 2 diabetes mellitus [8] and acts by stimulating pancreatic β-cells to produce more insulin and lower the blood glucose level (BGL). It has shown several advantages such as being highly protein bound, long-acting, and allowing for concomitant use with insulin. However, the drawback for the use of Glimepiride as oral dosage forms is attributable to its low aqueous solubility and slow dissolution rate, which lead to low oral bioavailability [9, 10]. The molecular weight of Glimepiride is 490.616 g/mol with an octanol/water partition coefficient of 3.5. It is completely absorbed after oral administration, [11] short half-life of ~5 h due to the extensive hepatic oxidative metabolism to its major metabolite, cyclohexyl hydroxy methyl derivative (M1) [12,13].

The purpose of the present work was to develop a transdermal formulation of Glimepiride, which increases patient compliance and enhances the bioavailability by using polymers and permeation enhancers.

MATERIALS AND METHODS:

Materials: Glimepiride was a gift sample from USV Limited, Khed, Ratnagiri, Maharashtra, India. Tristearin was purchased from TCI Pvt. Ltd. India. Soya lecithin was obtained as a gift sample from A. B. Enterprises, Mumbai, India. Tween 80 is obtained from S.D. Fine chemical limited, Bangalore.

Glassware: Various glassware is used such as a pipette, micropipette, measuring cylinder, Petri dish, beaker, funnel, sampling vials, volumetric flask, and Hamilton syringe, *etc*.

Instruments: Various types are used, such as UV double beam spectrophotometer, HPLC, Magnetic stirrer, digital weighing balance, melting point detector, and hot air oven, *etc*.

Methods:

Preparation of Transdermal Patches: Glimepiride loaded transdermal patches containing different ratios of HPMC K100M, and Eudragit RS100 were prepared by solvent casting method. The requisite ratios of polymers were weight and were allowed to swell for 6 h in methanol-dichloromethane (1:1) solvent mixture. Plasticizer such as PEG-400 was incorporated at 30% w/w of dry polymer weight, and permeation enhancer such as propylene glycol and dimethylsulfoxide (DMSO) was incorporated at 40% (1:1) w/w of the dry polymer weight.

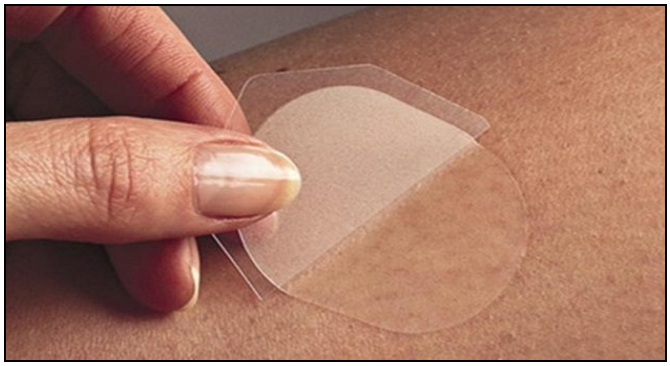

FIG. 1: TRANSDERMAL PATCHES

The calculated amount of Glimepiride was mixed with a homogenous polymer solution and poured into aluminum foil wrapped glass ring as mold (28.26 cm^2). A funnel was placed over the mold in an inverted position to control the rate of evaporation. The casting solvent mixture was allowed to evaporate overnight at room

temperature. The dried patches were cut into required size (3.14 cm^2) and wrapped in aluminum foil. Then, these Patches were kept in a desiccator containing a saturated solution of $CaCl_2$ as a desiccant, at room temperature before use [14, 15].

Identification and Characterization of Drug: Drug Identification Test (Organoleptic Property of the Drug): Drug (Glimipride) was physically characterized based on color, order, and taste. All these parameter ware recorded and compared with standard.

Melting Point Determination-(Capillary Melting Method): The temperature at which the solid and liquid phase is in equilibrium is called the melting point of the substance. A melting point determination is a good indication of purity since the presence of a relatively small amount of impurities can be detected by lowering as well as widening in melting point range. The melting point of the Glimepiride was determined by a capillary method using digital melting point apparatus (Jyoti Scientific Industry Gwalior MP).

Infrared Spectroscopy: An FTIR spectrum of Glimepiride was obtained by using FTIR spectrophotometer (IIT Kanpur). A pellet was prepared by using Tween80 and drug sample in the ratio of 10:1 by applying high pressure as 15 ton. The prepared pellet of tween 80 with the drug was examined under infrared spectrophotometer and compared with standard reference spectra of Glimepiride.

Ultraviolet Spectroscopy: UV spectral analysis was carried out for the identification of Glimepiride. A stock solution of Glimepiride was prepared by accurately weighing 10 mg of Glimepiride and dissolved in 10 ml ethanol in a volumetric flask, volume 100 ml with distilled water. To determine the absorption maxima (λ_{max}) for Glimepiride stock solution (10µg/ml) was scanned between 226 nm using double beam UV spectrophotometer.

Solubility Study: The solubility study of drug was prepared in different solvent (*e.g.*, distilled water, ethanol, methanol, methylene chloride, dimethyl formamide). Excess amount of drug was added to different solvent till the solution become saturated, and this volumetric flask were shaken by a mechanical shaker (Jyoti Scientific Industry Gwalior MP.) for 24 h under constant vibration at room temperature. The prepared saturated solution was filtered diluted and then analyzed by UV Spectrophotometer double beam (Shimadzu-1700 Japan).

Determination of Partition Coefficient: Partition coefficient drug was determined by allowing 10 mg of the drug to equilibrate in a mixture of *n*-octanol / water containing 100 ml of each by shaking on vortex mechanical shaker for 24 h and then starring it overnight at 37 ± 2 ºC in a separating funnel. The two layers were separated, and the concentration of drug in the two layers was determined by the UV spectrophotometer and the formula as given below.

$$Po/w = \frac{\text{The concentration of drug in } n\text{-octanol}}{\text{The concentration of drug in water}}$$

Drug-Polymer Interaction Studies: The identity and purity of excipients sample was determined by scanning the sample of excipients on FTIR spectra photometer. The FTIR spectra showed the characteristic peaks which are identical with ranges of the functional group of the excipients respectively, spectra of a mixture of Glimepiride, soya lecithin, tween 80 and tristearin.

Preparation of Standard Curve:

A) Standard curve of Glimepiride in Methanol:

a) Preparation of Stock Solution: According to British Pharmacopoeia, Glimepiride (10 mg) was accurately weighed and transferred in a 100 ml volumetric flask and dissolved in a small amount of methanol by shaking gently, and volume was made up to 100ml with methanol in a volumetric flask. The resultant solution of concentration of 100 µg/ml was formed. 10 ml of this solution was taken in 100ml volumetric flask, and volume was made up with methanol to form stock solution (10 µg/ml).

b) Determination of λ_{max} of Glimepiride: For the determination of λ_{max} 1 ml of stock solution was diluted to 10 ml and this 10 µg/ml was scanned in the range from 200-400 nm using Shimadzu 1700 spectrophotometer.

c) Preparation of Calibration Curves: The calibration curves of Glimepiride were prepared in differed media. The aliquots of 1, 2, 3,..10 ml of

stock solution (10 µg/ml) were transferred quantitatively into a series of 10 ml volumetric flasks and volumes were made up 10 ml to solve concentration ranging 1 to 10 µg/ml. The absorbance of these solutions was determined at λ_{max} 226 nm against a blank. The data were linearly regressed, and various statistical parameters were calculated and are presented.

B) Standard Curve of Glimepiride PBS pH 7.4:

A) Preparation of Buffer Solution (pH 7.4): Disodium hydrogen orthophosphate (2.38) potassium dihydrogen orthophosphate (0.19) and sodium chloride (8.0) were mixed in about 100 ml of distilled water, and the volume was made up 1000 ml with distilled water, the pH of was adjusted to 7.4 immediately before use with 0.1 hydrochloride acid or 0.1 NaOH as required.

b) Preparation of Stock Solution: Glimepiride (10mg) was accurately weighed and dissolved in ethanol in 100 ml volumetric flask, and volume was made up to 100 ml with ethanol. Then 10 ml of this solution was withdrawn and diluted up to 100 ml with ethanol in a volumetric flask to obtain 10 µg/ml solution.

λ_{max} Determination: For the determination of λ_{max}, 1ml of stock solution was diluted to 10 ml, and this 10 µg/ml was scanned in the range from 200-400 nm using Shimadzu 1700 spectrophotometer.

Construction of Calibration Curves: The calibration curves of Glimepiride were prepared in the differed medium. The aliquots of 1, 2, 3,. .10 ml of stock solution (10 µg/ml) were transferred quantitatively into a series of 10 ml volumetric flasks and volumes were made up 10 ml to produce a solution of concentration ranging 1 to 10 µg/ml.

The absorbance of these solutions was determined at λ_{max} 226 nm against a blank. The data were linearly regressed, and various statistical parameters were calculated and are presented. The linearly regressed curve is shown.

Drug Excipients Interaction Study: The drug excipients interaction study was carried out by IR spectroscopy. The IR spectrum of a combination of drug and various excipients to be used in the formulation was obtained using FTIR spectro-photometer (Shimadzu, Japan) and compared with individual spectra of drug and excipients to investigate any interaction.

Evaluation Parameters of Transdermal Patch:

Folding Endurance: A strip of a specific area (1.5×1cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film was folded at the same place without breaking gave the value of the folding endurance [16].

Tensile Strength: The tensile strength of the patch was evaluated by using the tensiometer (Erection and instrumentation, Ahmadabad). It consists of two load cell grips. The lower one was fixed, and the upper one was movable. Film strips with dimensions of 1.5×1 cm were fixed between these cell grips, and force was gradually applied till the film broke. The tensile strength was taken directly from the dial reading in kg [18].

Thickness: Patch thickness was measured using a digital micrometer screw gauge at three different places, and the mean value was calculated [16].

Drug Content: A specified area of the patch (1.5 × 1cm) was dissolved in 100mL methanol and shaken continuously for 24 h. Then the whole solution was ultrasonicated for 15 min. After filtration, the drug was estimated spectrophotometrically at a wavelength of 226 nm and determined the drug content [17].

Percentage Moisture Content: The prepared films were weighed individually and kept in a desiccator containing fused calcium chloride at room temperature for 24 h. After 24 h, the films were reweighed and determined the percentage of moisture content from the below-mentioned formula: [16]

Percentage moisture content = (Initial weight-Final weight) / Final weight × 100

RESULTS AND DISCUSSION:

Drug Identification Test (Organoleptic Property of the Drug): Physical appearance of the drug sample under investigation was found to be white powder and odour less, which was similar as reported in the literature.

Melting Point: Melting point of the drug was determined by capillary method and found to be as reported (138-140 ºC).

TABLE 1: ORGANOLEPTIC PROPERTY OF DRUG

S. no.	Physiochemical properties	Inference
1	Colour	White
2	Nature	Crystalline powder
3	Odor	Odorless

Infrared Spectroscopy: FTIR Spectrum of the drug was obtained by potassium bromide disk method using (FTIR IIT Kanpur). The principle peaks of the drug were identified and matched with the standard FTIR of the drug.

Confirming the identity and purity of the drug showed in **Fig. 2**, **3**, **4**.

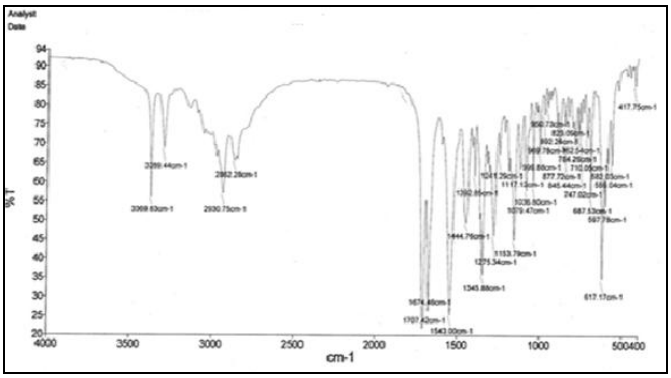

FIG. 2: FTIR SPECTRA OF DRUG

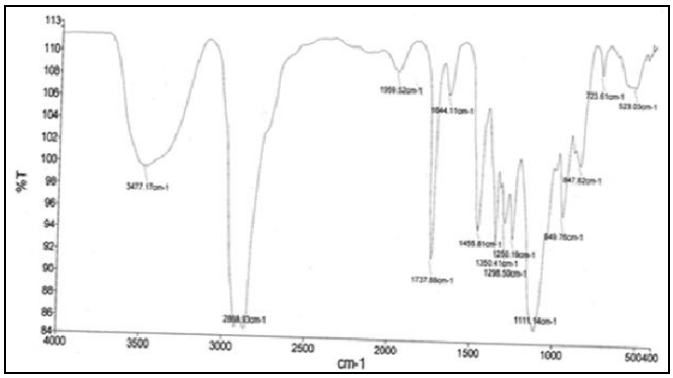

FIG. 3: FTIR SPECTRA OF POLYMER

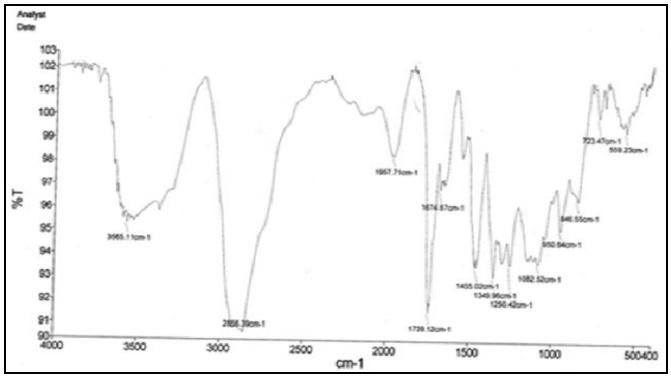

FIG. 4: FTIR SPECTRA OF DRUG AND POLYMER

TABLE 2: FTIR SPECTRA INTERPRETATION

S. no.	Wave no. Peak in cm^{-1}	Interpretation
1	3368.45 cm^{-1}, 3286.48 cm^{-1}	Due to N-H stretching for urea
2	3049.25 cm^{-1}	Aromatic stretch
3	2982.71 cm^{-1}	Aliphatic C-H stretching
4	1705.92 cm^{-1}	C=O stretching
5	1674.10 cm^{-1}	C=O stretching
6	1345.26cm^{-1}, 1154.32 cm^{-1}	Due to sulphonamide groups
7	1079.90 cm^{-1}	C-N-stretching
8	823.55 cm^{-1}	P- distributed aromatic drug

The possible interaction between drug and polymers were studied by FTIR spectroscopy. It was clear that there were no significant differences in IR peaks of drug alone and drug with a polymer which proved the absence of any possible interaction between the drug and polymers.

Standard calibration curve of Glimepiride was prepared in ethanol, and pH 7.4 PBS are shown in **Fig. 5**. The calibration curve was linear in the range 1-10 µ/ml in all cases, and hence, this range obeys the Beer-Lamberts low. The correlation coefficient value was greater than 0.99, indicating excellent linearity of the data.

Ultraviolet Spectroscopy: UV spectrum of Glimepiride was obtained by scanning the 10 µg/ml solution of drug ethanol between 200-400 nm range using. UV spectrophotometer Shimadzu 1700 (Japan). λ_{max} was found at 226nm for Glimepiride and showed in **Fig. 5**.

Solubility Studies: Solubility of Glimepiride in various Solvent: Solubility study of drug was prepared the drug found to be soluble in methanol, ethanol, and distal water in slightly soluble. Dimethylformamide free soluble.

Partition Coefficient of Glimepiride in Solvent System: Partition-coefficient of Glimepiride was determined by shake flask method for *n*-octanol /

water, and *n*-octanol / PBS found to be 0.726 and 0.899. This concludes that the drug is hydrophobic/ lipophilic in nature.

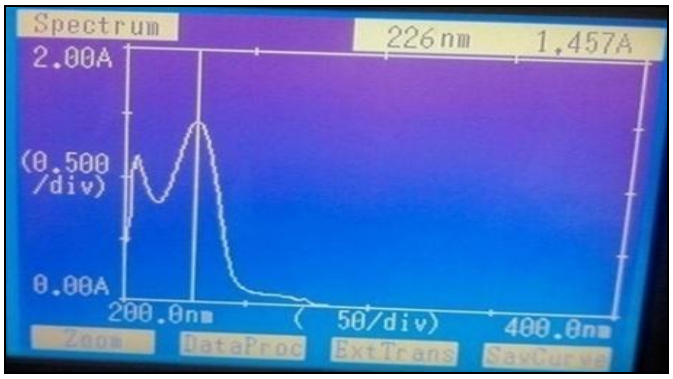

FIG. 5: UV SPECTRA OF GLIMEPIRIDE

TABLE 3: SOLUBILITY STUDY OF DRUG

Solvent	Inference
Water	Insoluble
ethanol	Soluble
Methanol	Slightly soluble
PBS	Soluble

TABLE 4: PARTITION COEFFICIENT OF DRUG

S. no.	Medium	Partition coefficient
1	*n*-octanol/distilled water	0.726
2	*n*-octanol/PBS(7.4)	0.899

Calibration Curve of Glimepiride in Distilled Water Using Co- Solvency of Ethanol:

TABLE 5: CALIBRATION CURVE DATA OF GLIMEPIRIDE IN DISTILLED WATER AT λ_{max} 226 nm AND OPTICAL CHARACTERISTICS OF GLIMEPIRIDE IN DISTILLED WATER

Concentration (µg/ml)	Absorbance (nm)
0	0.000
1	0.018
2	0.026
3	0.038
4	0.052
5	0.063
6	0.079
7	0.091
8	0.105
9	0.117
10	0.131

TABLE 6: STATISTICAL PARAMETERS OF GLIMEPIRIDE IN DISTILLED WATER

Parameter	Values
λ_{max}	226 nm
Beer's law limit	1-10
Regression equation	Y=0.012x+0.000
Slope	0.012
Intercept	0.000
Correlation coefficient	0.998

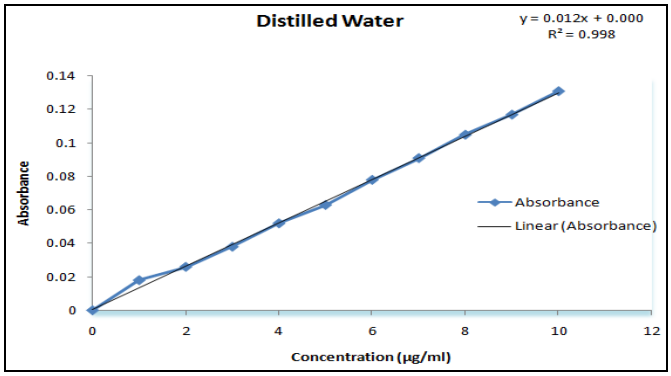

FIG. 6: LINEARLY REGRESSED CALIBRATION CURVE OF GLIMEPIRIDE IN DISTILLED WATER AT λ_{max} 226nm

Calibration Curve of Glimepiride in Phosphate Buffer Solution (PBS) pH 7.4 Using Co-Solvency of Ethanol:

TABLE 7: CALIBRATION CURVE OF GLIMEPIRIDE IN PHOSPHATE BUFFER SOLUTION (PBS) pH 7.4 AT λ_{max} 226 nm

Concentration	Absorbance
0	0.000
1	0.029
2	0.047
3	0.069
4	0.083
5	0.109
6	0.131
7	0.159
8	0.179
9	0.185
10	0.198

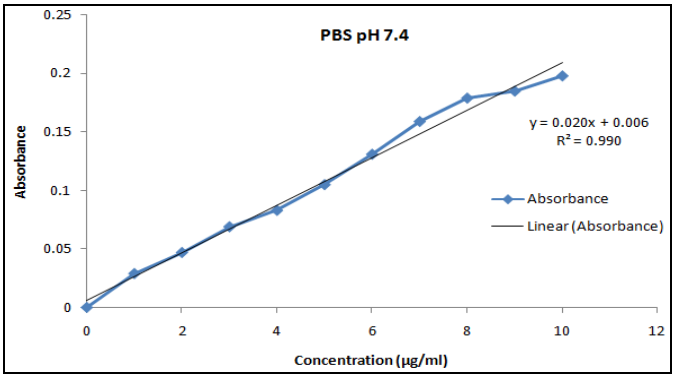

FIG. 7: LINEARLY REGRESSED CALIBRATION CURVE OF GLIMEPIRIDE IN PHOSPHATE BUFFER SOLUTION (pH = 7.4)

TABLE 8: STATISTICAL PARAMETERS OF GLIMEPIRIDE IN PHOSPHATE BUFFER SOLUTION (pH=7.4)

Parameter	Values
λ_{max}	226 nm
Beer's law limit	1-10
Regression equation	Y=0.020x+0.006
Slope	0.020
Intercept	0.006
Correlation coefficient	0.990

Calibration Curve of Glimepiride in Ethanol at λ_{max} 226 nm:

TABLE 9: CALIBRATION CURVE DATA OF GLIMEPIRIDE IN ETHANOL AT λ_{max} 226 nm

Concentration (µg/ml)	Absorbance (nm)
0	0.000
1	0.080
2	0.141
3	0.210
4	0.278
5	0.350
6	0.410
7	0.492
8	0.551
9	0.650
10	0.701

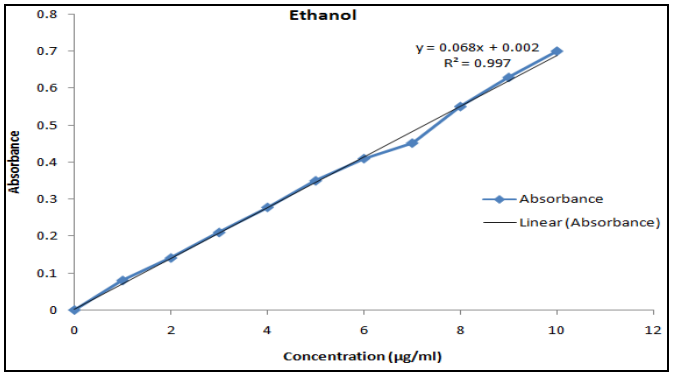

FIG. 8: LINEARLY REGRESSED CALIBRATION CURVE OF GLIMEPIRIDE IN ETHANOL AT λ_{max} 226 nm

TABLE 10: STATISTICAL PARAMETERS OF GLIMEPIRIDE IN ETHANOL

Parameter	Values
λ max	226 nm
Beer's law limit	1-10
Regression equation	Y=0.069x+0.002
Slope	0.069
Intercept	0.002
Correlation coefficient	0.999
Flow index	0.231

Evaluation of Glimepiride Loaded Transdermal l Patch: Determination of drug content, pH, spreadability and viscosity.

TABLE 11: EVALUATION OF THE VARIOUS PARAMETER OF DRUG CONTENT pH SPREADABILITY

Parameters	Observation
Drug content	63.43 ± 0.64
pH	6.9
Spreadability (cm)	7.1
Viscosity at 5 rpm (mPas)	22.4 x 10^5
Consistency index (dyn/cm^2)	21.63 x 10^6
Flow index	0.231

CONCLUSION: Transdermal patches of Glimepiride using polymers like tristearin and soya lecithin in various proportions and combinations showed satisfactory physicochemical characteristics. The proportional amounts of various hydrophilic polymers in various formulations have an influence on drug release from these formulated Glimepiride transdermal patches. From the present study, it can be concluded that transdermal drug delivery system for Glimepiride with tristearin and Eudragit RS100 meet the ideal requirement for transdermal devices which can be a good way to bypass the extensive hepatic first-pass metabolism and increase bioavailability.

Transdermal patches of Glimepiride may provide sustained transdermal delivery for prolonged periods in the therapy of Diabetics, which can be tristearin and soya lecithin of moderate level useful for the preparation of sustained release matrix transdermal patch formulation.

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CONFLICT OF INTEREST: Nil

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