Design, Development And Evaluation Of Transdermal Drug Delivery System For Treatment Of Diabetes

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Abstract

The current research aims to formulate and evaluated Cinnamaldehyde transdermal patches to treat diabetes. A good penetration enhancer Oleic Acid, would improve drug delivery from various polymer-based transdermal patches. Transdermal patches of the matrix type were made by solvent casting techniques using various polymer PVP K30, HPMC K100, and solvent. All prepared formulations were tested for folding endurance, weight variation, thickness, drug content, moisture content, moisture loss, in vitro drug release and in vivo studies. Batch TDP1 was optimised formula from all formulation batches shows zero order release for 24 hours, with a cumulative percentage of drug diffusion of 97.68% from 2cm² patches. It has been determined that polymer concentration HPMC films showed better release which may be attributed to the reason of high water vapour permeability of HPMC films for enhancing diffusion rate of drug through rat skin, oleic acid were incorporated as permeation enhancers in the HPMC films since they showed better release. It allows for controlled drug release from the patch. Drug content of the patches was found to be more than 98%. Variations in flux and Diffusion Coefficient were observed among various formulations. The drug–polymer interaction results suggested no interaction between drug and polymers. The in vitro results revealed that the patches successfully prevented the hyperglycaemia and they were also effective on chronic application. The transdermal route exhibited negligible skin irritation and produced better improvement with all the tested in vitro parameters compared to oral administration.

Keywords: Transdermal patch, PVP K30, Cinnamaldehyde, In-vitro, In-vivo, Diabetes

1. INTRODUCTION

Diabetes was formerly known as "honey urine." It has now been recognised as a devastating and fatal disease. Chronic hyperglycaemia is a common symptom of diabetes mellitus, a group of metabolic illnesses [1]. Diabetes is caused by either a lack of insulin production or a lack of insulin activity. Depending on the disease's pathophysiology and clinical signs at the time of diagnosis, diabetes may be categorised into many kinds. Deficiency of insulin is the primary cause of type 1 diabetes mellitus (T1DM), which is caused by the death of beta cells in the islets of Langerhans [2]. Type 2 diabetes mellitus, formerly known as non-insulin-dependent diabetes mellitus or T2DM for short. This kind of diabetes is caused by a combination of hereditary and environmental causes, resulting in insulin insufficiency and insulin resistance [3]. Cinnamaldehyde, one of the active components derived from Cinnamon, has been used as a natural flavourant and fragrance agent in kitchen and industry. Emerging studies have been performed over the past decades to evaluate its beneficial role in management of diabetes and its complications. Cinnamaldehyde exhibits glycolipid lowering effects in diabetic animals by increasing glucose uptake and improving insulin sensitivity in adipose and skeletal muscle tissues, improving glycogen synthesis in liver, restoring pancreatic islets dysfunction, slowing gastric emptying rates, and improving diabetic renal and brain disorders [4].

The fundamental goal of a transdermal medication delivery system is to deliver pharmaceuticals into the systemic circulation through the skin at a predefined pace with little fluctuation between and within patients. The most significant advantages provided by the following are some examples of transdermal medication delivery: increased bioavailability and effect duration, resulting in a reduced dosing frequency, plasma levels are more uniform, and adverse effects are reduced [5]. Transdermal patches are a type of patch that is applied to the skin. It’s proved helpful in minimising the effects of first-pass medication degradation. The majority of transdermal patches are made to release the active ingredient. For several hours to days following application to the skin, the chemical has a zero-order rate. Drugs penetrate multiple layers of skin and permeate the epidermis into systemic circulation in transdermal patches. Some substances, such as dimethylsulfoxide, azone, pyrrolidiones, urea, and fatty acids, Polyols, can improve medication penetration through the skin [6]. In general, once medication molecules break the stratum corneal barrier, they move swiftly and easily into deeper dermal layers, allowing for systemic uptake. In this research studies, we reported the formulation and evaluation of transdermal patch of cinnamaldehyde, which exhibited improved in vivo performance compared to oral administration. In order to enhance the in vivo effectiveness of cinnamaldehyde, a suitable candidate for transdermal delivery, we have
formulated the matrix transdermal systems of cinnamaldehyde using HPMC (hydrophobic) and polyvinylpyrrolidone K (hydrophilic) and evaluated with respect to various in vitro and preclinical in vivo parameters[7].

2. MATERIALS AND METHODS
2.1 Materials
Cinnamaldehyde was received as a gift sample from Loba Chemie Pvt. Ltd. Hydroxy Propyl Methyl Cel- lulose K 100 was obtained from Department of Pharmaceutical Science, West Bengal. PVP K30 was obtained from Spectrochem Pvt. Ltd., Mumbai. Oleic Acid was obtained from Loba Chemie Pvt. Ltd. Menthol was used of Analytical grade and All other materials and chemicals used were of either pharmaceutical or analytical grade.

2.2 Methods
Design of formulations variables and development of medicated patches (Cinnamaldehyde)
The medicated patches were prepared by solvent casting technique employing glycerine as a substrate. The casting solution were prepared by dissolving appropriate polymers, drug, plasticizers, and permeation enhancer (5% of the total weight of polymer) were incorporated in suitable solvents according to factorial designed and solution was mixed using magnetic stirrer till to get the clear homogeneous mixture. The solution was then poured into the petridish and allows drying and solvent evaporation was controlled by placing an invert funnel over the petridish [8]. These were left at room temperature for one day. patches could be retrieved intact by slowly lifting from the petriplate and packed in the aluminum foil and kept in the desiccators until used. A film layer was prepared and cut into even pieces of desired size (5cm x 5cm). 9 Formulations having different proportions of oleic acid and amount of HPMC were tabulated in Table 1.

2.3 Preliminary studies
2.31 Determination of \( \lambda_{max} \)
A diluted solution of the API (cinnamaldehyde) in phosphate buffer (pH 7.4) was scanned from 400-200nm against phosphate buffer (pH 7.4) blank to obtain wave length of maximum absorbance. At 287 nm wave length cinnamaldehyde give maximum absorbance of 0.206. So, the \( \lambda_{max} \) value of cinnamaldehyde is at 287 nm shown in figure 1.

2.3.2 Preparation of calibration curve for cinnamaldehyde
Standard stock solution was prepared by dissolving 1 drop (32 mg) of API in 100 ml of ethanol to get a concentration of 0.32 mg/ml. Further the solution was diluted up to 100 ml with the phosphate buffer (pH 7.4) employing 3 ml of the above solution to obtain a solution with concentration of 1mg/ml. Preparation of Standard curve (using \( \lambda_{max} \) value from previous study at pH 7.4). Aliquots of stock solution were further diluted with phosphate buffer pH 7.4 to get working solution of 0, 5, 10, 20, 30, 40, 50 mcg/ml. The diluted solution was taken into UV- Spectrophotometer for getting the absorption against the blank solution at \( \lambda_{max} \) of 287 nm. The absorbance at 287 nm wavelength was measured spectrophotometrically. Table 4 shows the absorbance value. Figure no 3 shows standard calibration curves with a slope of 0.0015 and a regression coefficient of 0.9921. The curve was found to be linear in the range 5- 50 μg/ml.

2.3.3 Drug-polymer compatibility studies
FTIR- The drug-polymer compatibility studies were carried out using FTIR-Spectrophotometer using SHIMADZU FTIR-8400S. the spectrum was recorded in the region of 4000-400 cm\(^{-1}\). There is no any interaction shown in study. Differential Scanning Calorimetry (DSC) – DSC was performed on pure drug, excipients and composition official formulation. DSC measurements were done on a Shimadzu DSC60 having TA60 software, Shimadzu, Japan. They are heated from temperature of 25°C to 300°C C at a heating rate of 10°C per minutes, under constant nitrogen purging and no any interaction shown in drug mixture.

<table>
<thead>
<tr>
<th>Ingredients (gm)</th>
<th>TDP1</th>
<th>TDP2</th>
<th>TDP3</th>
<th>TDP4</th>
<th>TDP5</th>
<th>TDP6</th>
<th>TDP7</th>
<th>TDP8</th>
<th>TDP9</th>
</tr>
</thead>
<tbody>
<tr>
<td>drug</td>
<td>0.106</td>
<td>0.106</td>
<td>0.106</td>
<td>0.106</td>
<td>0.106</td>
<td>0.106</td>
<td>0.106</td>
<td>0.106</td>
<td>0.106</td>
</tr>
<tr>
<td>HPMC</td>
<td>3.22</td>
<td>0.079</td>
<td>1.5</td>
<td>2.25</td>
<td>3</td>
<td>2.25</td>
<td>2.25</td>
<td>1.5</td>
<td>3</td>
</tr>
<tr>
<td>pvpk-30</td>
<td>1.00</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>oleic acid</td>
<td>2.00</td>
<td>0.079</td>
<td>1.5</td>
<td>2.25</td>
<td>3</td>
<td>2.25</td>
<td>2.25</td>
<td>1.5</td>
<td>3</td>
</tr>
<tr>
<td>glycerine</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>distilled water</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

2.4 Evaluation of transdermal patches
2.4.1 Folding endurance:
The folding endurance measured manually for the prepared patches. It is determined through folding a small strip of film (5cm x 5cm) persistently at the identical area until it breaks and to develop visible cracks, gave the assessment of folding endurance. Patch folding endurance was found to be satisfactory between 226±1.52 and 505±1.52.

2.4.2 Weight Variation
Three patches from each batch were accurately weighed by using a digital weighing balance. The average weight and the standard deviation values were calculated from the individual weight. The weight of cinnamaldehyde patches ranged from 178±0.01 to 390±0.036.
2.4.3 Thickness of the patches
The thickness of the transdermal films was measured at three different points using a screw gauge and the average thickness values and standard deviation were calculated for each formulation. The thickness of cinnamaldehyde patches ranged from 0.20±0.020 to 0.458±0.030.

2.4.4 Drug Content
A specific film area (1 x 1 cm$^2$) was cut and dissolved in sufficient amount of phosphate buffer saline. The volume was made up to 10ml and 1ml was withdrawn from this solution and further diluted to 10ml. After adding suitable reagent and dilution the solution was filtered by Whatman’s filter membrane, and the absorbance of the solution was found out at 251nm by using UV-Vis spectrophotometer. From the absorbance and dilution factor, the drug content in the film was calculated. Average drug content of three transdermal patch was ranged from 91±0.39 to 98±0.20 percent, indicating passable drug content in patches.

2.4.5 Percentage Moisture content
The films were weighed accurately and placed in the desiccators containing 100ml of saturated solution of aluminium chloride. The individual films were weighed repeatedly and the patches were taken out, after 3 days, or until a stable weight of film was achieved. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight [9].

$$\text{Percentage of moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

The moisture content in the patches was ranged from 6.142±0.49 % to 9.542±0.15 %.

2.4.6 Percentage Moisture Loss
The patches were weight accurately and kept in a desiccators containing activated silica. The individual films were weighed repeatedly and the patches were taken out, after 3 days or until a stable weight of film was achieved. The percentage of moisture loss was calculated as the difference between initial and final weight with respect to initial weight[9].

$$\text{Percentage of moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

The moisture loss in the patches was ranged from 3.098±0.53 % to 6.39±0.28%.

2.5 In-Vitro Study of Transdermal Patches
In-vitro studies were performed by using a Franz diffusion cell with a receptor compartment capacity of 30 mL. In vitro drug release studies were carried out using synthetic cellophane membrane. The prepared formulations 2cm$^2$ were cut and fixed on to the membrane in the donor compartment and were uniformly spread onto the cellophane membrane. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm; the temperature was maintained at 32 ± 0.5 °C. The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer pH 7.4 at each sample withdrawal. The cumulative percentages of drug permeated per square centimeter of patches were plotted against time.

2.6.1 Determination of Flux and Diffusion Coefficient
The flux (µg/cm²/hr) of drug was calculated from the slope of the plot of the cumulative amount of drug permitted per sq.cm at steady state against time using linear regression analysis as shown in table 10. The drug diffused through the dialysis membrane can be considered to calculate the steady state permeability coefficient (Kp) using the following equation:

$$\text{Kp} = \frac{J}{C}$$

Where, $J$ = Flux at steady state. $C$ = Drug concentration in donor compartment.

2.6.3 Optimization
Optimization of transdermal patch will be done on the basis of % of cumulative drug release, flux and folding endurance of patches.

2.6 Stability Studies of Optimized Formulation
To perform the stability of optimized formulation, samples were sealed in aluminum foil and stored at room temperature. The studies were conducted for six months at a temperature of 40°C and 75% relative humidity.

2.7 In vivo studies
2.7.1 Determination of antidiabetic activity of Cinnamaldehyde transdermal patches on rat model
The Albino rats weighing 150-200 gm were selected for in vivo pre-clinical studies. The rats were housed in propylene cages with free access to water and standard rat pellet diet. Water was given ad libitum during the entire period of the study. They were maintained at a temperature of 25±1°C and a relative humidity of 45-55% with a 12 hr light or dark cycle. They were acclimatized to the laboratory conditions before carrying out experimental work in a well-ventilated animal house under natural photoperiod conditions for a period of 1 week. The protocol of in vivo experiments was approved by the Indian Animal Ethical Committee. The hair on back side of the rat was removed completely on the previous day of the experiment.
2.7.2 Induction of diabetes mellitus
Rats weighing 150-200 g were selected and fasted for a 16 h period for experiments and allowed an excess ad libitum. Experimental Diabetes was induced by a single intraperitoneal injection of freshly prepared STZ (55 mg/kg) in 0.1 M citrate buffer (pH 4.5). After 4 days blood glucose level of each animal were determined and rats with blood glucose level above 200 mg/dl were considered as diabetic rats and the formulated transdermal patches were evaluated for anti-diabetic activity in overnight fasted diabetic rats [10].

2.7.3 Experimental design
Rats were divided into four groups, each group comprised of six rats. (6 normal; 18 STZ-diabetic surviving rats) The treatment of rats was as follows shown in table 2:
Group I was considered as a Normal group, received vehicle only Group II was considered as Disease control group, received 0.1 M citrate buffer (pH 4.5).in dis-tilled water was used as a vehicle.
Group III was considered as Standard treatment group (Cinnamaldehyde 20 mg/kg)
Group IV was considered as Test treatment group received Optimized transdermal patch (TDP1)
The blood samples were collected by retro orbital method and the serum was separated by centrifugation at 3000 rpm after 30 min of stabilization. Biochemical parameter like glucose, cholesterol, Protein, HDL cholesterol, LDL cholesterol, and triglyceride were measured.

2.7.4. Glucose parameter
The blood glucose level was measured in normal and experiment group at 0 day, 15th days and 30th days of treatment. A body glucose level for each group of rat was recorded for last days during the period of experiment in glucometer (one touch select simple). The difference between mean glucose levels in each group was calculated to measured the change in the glucose level in 30th day as shown.

2.7.5 Cholesterol parameter
The antidiabetic effect of Transdermal patches was observed through determination of lipid profile in serum. Body serum total cholesterol for each group of rats was recorded for last days during the period of experiment. The difference between mean serum total cholesterol in each group was calculated to determine the change in the serum total cholesterol in 30th day shown in in results below

2.7.6 Protein level, Albumin, Urea parameters
The Total protein, Albumin, Urea levels in normal and streptozotocin induced diabetic rat was determined through body serum for last days during the period of experiment. The difference between mean serum total Protein level, Albumin, Urea level in each group was calculated in 30th day shown in results below.

2.7.7 Skin irritation test
The pre-clinical study for skin irritation was conducted using male Albino rats weighing about 2.5-3.0 gms of 24 months of age. The animals were kept in animal cages for 24 hrs. Patches were withdrawn after 24 hrs and examined for erythema, eschar and edema. scale for erythema and edema formation. The results showed that the transdermal systems produced negligible erythema and edema as shown in table 6.

3. RESULT AND DISCUSSION

### Figure 1 Calibration Curve Of Cinnamaldehyde

![Calibration Curve Of Cinnamaldehyde](image)

3.1. Evaluation of transdermal patch

### Table 2: In-Vitro Study Of Transdermal Patch TDP1 To TDP9

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>CUMULATIVE PERCENT DRUG RELEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TDP1</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>3.4 ± 0.12</td>
</tr>
<tr>
<td>4</td>
<td>3.4 ± 0.12</td>
</tr>
<tr>
<td>6</td>
<td>3.4 ± 0.12</td>
</tr>
<tr>
<td>8</td>
<td>3.4 ± 0.12</td>
</tr>
<tr>
<td>10</td>
<td>3.4 ± 0.12</td>
</tr>
<tr>
<td>12</td>
<td>3.4 ± 0.12</td>
</tr>
<tr>
<td>24</td>
<td>3.4 ± 0.12</td>
</tr>
</tbody>
</table>
Table 3. Drug Release Kinetics (Cinnamaldehyde)

<table>
<thead>
<tr>
<th>S.no.</th>
<th>Formulation</th>
<th>Zero order ($R^2$)</th>
<th>First order ($R^2$)</th>
<th>Higuchi model ($R^2$)</th>
<th>Korsmeyer peppas model (n) ($R^2$)</th>
<th>Hixson crowell model ($R^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TDP1</td>
<td>0.9855</td>
<td>0.967</td>
<td>0.9842</td>
<td>0.698</td>
<td>0.8974</td>
</tr>
<tr>
<td>2</td>
<td>TDP2</td>
<td>0.993</td>
<td>0.9632</td>
<td>0.9812</td>
<td>0.604</td>
<td>0.8867</td>
</tr>
<tr>
<td>3</td>
<td>TDP3</td>
<td>0.9972</td>
<td>0.9211</td>
<td>0.9728</td>
<td>0.612</td>
<td>0.8647</td>
</tr>
<tr>
<td>4</td>
<td>TDP4</td>
<td>0.9706</td>
<td>0.9829</td>
<td>0.9824</td>
<td>0.678</td>
<td>0.9082</td>
</tr>
<tr>
<td>5</td>
<td>TDP5</td>
<td>0.9924</td>
<td>0.9632</td>
<td>0.9725</td>
<td>0.504</td>
<td>0.8573</td>
</tr>
<tr>
<td>6</td>
<td>TDP6</td>
<td>0.9925</td>
<td>0.9282</td>
<td>0.9763</td>
<td>0.589</td>
<td>0.876</td>
</tr>
<tr>
<td>7</td>
<td>TDP7</td>
<td>0.9806</td>
<td>0.97</td>
<td>0.9803</td>
<td>0.453</td>
<td>0.8743</td>
</tr>
<tr>
<td>8</td>
<td>TDP8</td>
<td>0.9931</td>
<td>0.9799</td>
<td>0.9761</td>
<td>0.223</td>
<td>0.8936</td>
</tr>
<tr>
<td>9</td>
<td>TDP9</td>
<td>0.9991</td>
<td>0.9768</td>
<td>0.9594</td>
<td>0.356</td>
<td>0.8384</td>
</tr>
</tbody>
</table>

All the value represented mean ± S.D (n=3)

Figure 2: Cumulative Drug Release Graph

Optimization of Formulation

In vitro release of cinnamaldehyde across dialysis membrane from TDP1 to TDP9 formulation was only 97.68, 85.08, 88.05, 92.68, 95.18, 90.58, 91.88 at the end of 24hrs. The flux was calculated from the slope of linear graph, and it was found to be 57.78, 45.46, 48.74, 51.75, 54.32, 49.12, 50.49, 41.18, 52.61μg/cm2/h × 10^-2, diffusion coefficient was 0.92, 0.72, 0.75, 0.81, 0.86, 0.77, 0.78, 0.64, 0.84 cm2/h × 10^-2 respectively. It was evident from the above result that there was a lower flux and lower diffusion rate through the dialysis membrane for TDP2 to TDP9. However, at the end of 24h, in vitro release of cinnamaldehyde across dialysis membrane from formulation. It was revealed from the above results that the TDP1 showed prolonged release of drug from the patches. The formulation of TDP1 containing HPMC and PVP-K30 in the amount of 3.22, 1.00 showed 97.68% of cinnamaldehyde release at the end of 24h study. The flux and diffusion coefficient was found 57.78 μg/cm2/h × 10^-2 and 0.92 cm2/h× 10^-2 respectively. The hydrophilic and swellable nature of the polymers which could affect the release of drug from the patches may be the reason for the maximum release of the drug from the optimized patch. The rapid diffusion of drug from the surface and consequent increase in the path length of diffusion may be the cause for controlled release of the drug from the patch.

HPMC films showed better release which may be attributed to the reason of high water vapour permeability of HPMC films for enhancing diffusion rate of drug through rat skin, oleic acid were incorporated as permeation enhancers in the HPMC films since they showed better release. The physicochemical properties of the formulation TDP1 depicted suitable formulation for the transdermal delivery. From the above criteria, TDP1 was hand-picked as an optimized formulation.

Stability studies

The stability studies were carried out for the optimized formulations, TDP1 at 40±2°C, 75±5% relative humidity for six months. The results shown in Table 5 indicated that there was no remarkable difference between the initial values and the values obtained during stability studies. The data, after stability period, of evaluation parameters of transdermal films were found nearly same as those of patch, before the stability period. It was conclude that the release of drug after stability period was same as before. Hence, stability study indicates that the formulation is quite stable.

Table 4. Stability Evaluation Of Optimized Formulation Of Cinnamaldehyde Formulation (TDP1)

<table>
<thead>
<tr>
<th>S. No</th>
<th>Parameter</th>
<th>Initial(0days)</th>
<th>1 Months</th>
<th>3 Months</th>
<th>6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Moisture loss</td>
<td>7.045±0.027</td>
<td>7.015±0.017</td>
<td>7.015±0.017</td>
<td>7.015±0.017</td>
</tr>
<tr>
<td>2</td>
<td>folding endurance</td>
<td>342±0.15</td>
<td>342±0.05</td>
<td>344±0.05</td>
<td>344±0.05</td>
</tr>
<tr>
<td>3</td>
<td>Drug content</td>
<td>98±0.20</td>
<td>97.58±0.20</td>
<td>97.58±0.20</td>
<td>97.58±0.20</td>
</tr>
<tr>
<td>4</td>
<td>Drug release</td>
<td>97.68±0.94</td>
<td>97.68±0.94</td>
<td>95.68±0.64</td>
<td>94.68±0.124</td>
</tr>
<tr>
<td>5</td>
<td>Weight Variation</td>
<td>19±0.0008</td>
<td>19±0.08</td>
<td>19±0.28</td>
<td>19±0.81</td>
</tr>
<tr>
<td>6</td>
<td>Tensile Strength</td>
<td>0.598±0.017</td>
<td>0.598±0.017</td>
<td>0.598±0.017</td>
<td>0.598±0.017</td>
</tr>
</tbody>
</table>
Figure 3. Drug Release After 1, 3, 6 Months Of Optimized Formulation

In vivo studies

Table 5: Effect Of Cinnamaldehyde Patch On Plasma Glucose Levels In Normal And Streptozotocin-Induced Diabetic Male Albino Rats

<table>
<thead>
<tr>
<th>Groups</th>
<th>Plasma glucose levels (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0th days</td>
</tr>
<tr>
<td>Normal(Liquid))</td>
<td>85.67±5.3</td>
</tr>
<tr>
<td>Disease control (Simple buffer)</td>
<td>315.9±2.10</td>
</tr>
<tr>
<td>Standard treatment (Liquid + Cinnamaldehyde 20 mg/kg)</td>
<td>224±2.10</td>
</tr>
<tr>
<td>Test treatment (Liquid + Optimized transdermal patch TDP1)</td>
<td>152.56±2.20</td>
</tr>
</tbody>
</table>

n=6, values are average of three of 6 reading ±standard deviation

Figure 4. Plasma Glucose Levels In Normal And Streptozotocin-Induced Diabetic Male Albino Rats

Figure 5. Plasma Total Cholesterol Levels In Normal And Streptozotocin-Induced Diabetic Male Albino Rats
DISCUSSION
The data of reduction of blood glucose levels by the formulated transdermal drug delivery systems in comparison with orally administered system in both normal and diabetic rats was shown. A significant blood glucose lowering effect was identified in oral and transdermal system treated animal groups within 30 days. Cinnamaldehyde when administered orally produced a percentage reduction of 133.26±6.15 with and 151.30±2.43 (diabetic rats, p<0.05 compared to diabetic control) in blood glucose levels in 30 days with optimized formulation. The blood glucose lowering response was gradual in case of transdermal system. Hypoglycemia was not noticed in the untreated group. A significant reduction in cholesterol level was identified in oral and transdermal system of Cinnamaldehyde treated animal groups within 30 days. 110.4±2.0 and 157.56±2.20 reduction in total cholesterol (mg/dl) was identified. Triglycerides (mg/dl) level was identified 17.58±2.50 with oral treatment of cinnamaldehyde. And 19.58±4.37 with optimized transdermal patch. 61.26±1.15 and 58.30±1.43 reduction in HDL level with oral and transdermal treatment was identified. 97 ± 1.45 and 75 ± 3.45 level was identified in LDL level in 30 days with oral and optimized formulation. Total Protein level (g/dl) in diabetic control with optimized formulation 6.08±0.04 was identified for cinnamaldehyde. Albumin level was 3.03±0.37, and urea level was 30.30±1.43 identified for transdrmal route. But from oral route total protein, albumin, urea, it was found to be 6.9±1.0 , 3.58±1.01 35.26±1.15 for cinnamaldehyde. negligible erythema and edema were shown in rat models.

CONCLUSION
The hydrophilic and swellable nature of the polymers which could affect the release of drug from the patches may be the reason for the maximum release of the drug from the optimized patch. The rapid diffusion of drug from the surface and consequent increase in the path length of diffusion may be the cause for controlled release of the drug from the patch. HPMC films showed better release which may be attributed to the reason of high water vapour permeability of HPMC films for enhancing diffusion rate of drug through rat skin, oleic acid were incorporated as permeation enhancers in the HPMC films since they showed better release. The physicochemical properties of the formulation TDP1 depicted suitable formulation for the transdermal delivery. From the above criteria, TDP1 was hand-picked as an best formulation. TDP1 was the optimized formulation showing unif orm thickness, good tensile strength, drug content uniformity and good folding endurane. The formulation TDP1 showed linear zero order release for 24 hours with cumulative % drug diffused of 97.68. % from 2 cm² patch. The present study showed that matrix transdermal patches of cinnamaldehyde exhibited better in vivo performance than oral cinnamaldehyde administration in rat as well reversing the diabetic complications. The clinical studies of these patches are shortly being undertaken in human volunteers to verify these findings.

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