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FORMULATION, DEVELOPMENT AND EVALUATION OF ANTIDIABETIC TRANSDERMAL DRUG DELIVERY SYSTEM OF GUAVA

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ABSTRACT
The transdermal drug delivery system (TDDS) is a cutting-edge method whose primary goals are to increase patient compliance, sustain medication release, and increase drug bioavailability. Among the different kinds of transdermal patches, matrix dispersion type systems distribute the medication and polymers in a solvent, allowing the solvent to evaporate and creating a uniform drug-polymer matrix. One of the novel drug delivery methods is the medicated transdermal patch system, which applies a prescribed dosage of medication to the skin's surface and then circulates it through the skin and into the bloodstream.With an insulin-independent mechanism, canagliflozin (CFZ), a member of a new class of sodium glucose co-transporter (SGLT II) inhibitors, has been extensively utilized in the treatment of type 2 diabetic mellitus (T2DM). SGLT II is a low-capacity/high-affinity Na +/K+ co-transporter that is mostly found in the kidneys' proximal convoluted tubules (PCT). It inhibits glucose reabsorption and promotes urine excretion of glucose as a result. The current project aims to create transdermal patches containing an anti-diabetic medication that increase canagliflozin's bioavailability.
Transdermal patches, permeability, solubility, moisture content, and pharmacological properties are the key words.

INTRODUCTION:
Drugs administered in the conventional dosage forms usually produce large range in fluctuations in plasma drug concentrations leading to undesirable toxicity or poor effectiveness. These factors as well as other factors such as repetitive dosing and unpredictable absorption, led to the concept of the controlled drug delivery system or therapeutic system. A dosage form that releases one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ is a controlled drug delivery system. The primary objectives of controlled drug delivery are to ensure safety and to improve efficacy of drugs as well as patient compliance. This is achieved by better control of plasma drug levels and less frequent dosing. Transdermal therapeutic systems are defined as self- contained discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the systemic circulation [1-2]The first Transdermal drug delivery (TDD) system, Transderm-Scop developed in 1980, contained the drug Scopolamin for treatment of motion sickness. The Transdermal device is a membranemoderated system. The membrane in this systemis a microporous polypropylene film. The drugreservoir is a solution of the drug in amixture of mineral oil and polyisobutylene. This study release is maintained over a three-day period [3] .

ADVANTAGES:

There are many advantages associated with Transdermal drug delivery systems[4-5] .

- The drugs by pass the hepatic and pre systemic metabolism thereby increasing bioavailability.
- Risks and inconveniences of IV therapy are avoided.
- Reduced dose frequency and predictable sustained and extended duration ofaction.
- Easy termination of drug therapy. It gives greater patient compliance due toelimination of multiple dosing intervals.
- Enhanced therapeutic efficiency by avoiding the peaks and troughs insystemic drug levels associated with conventional delivery.
- Self –administration is possible.

BASIC COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEMS

The components of Transdermal device include [6,7] .

- Polymer matrix
- Drug
- Permeation enhancers
- Other excipients
- Polymer Matrix

2. MATERIALS AND METHODS

Table 2: Materials used for formulation development of transdermal patch

Sr. No.	Chemicals	Supplier
1.	Canagliflozin	(Gift sample from Bioplus Life Science, Bangalore)
2.	HPMC	Ozone international, Mumbai
3.	RLPO	Evonic industries
4.	RSPO	Evonic industries
5.	PEG	Thomas beker (chemical)
6.	Disodium Hydrogen Phosphate	S. D. Fine Chem. Ltd., Mumbai
7.	Sodium Chloride	S. D. Fine Chem. Ltd., Mumbai
8.	Methanol	Qualigens Fine Chemicals, Mumbai
9.	Ethanol	Qualigens Fine Chemicals, Mumbai
10.	Chloroform	Qualigens Fine Chemicals, Mumbai

2.1 Preformulation characteristics:

The following properties of active pharmaceutical ingredients (API) wereinvestigated;

- Organoleptic properties
- Solubility Analysis
- Loss on drying
- Melting point
- UV Spectrophotometric analysis
- FTIR spectroscopy

2.1.1 Organoleptic properties:

Organoleptic properties of the drug substance are very important for designing thedosage form. The colour, odour and tests of the drug are characterized.

2.2.2 Solubility Analysis:

An important Physical-chemical property of a drug substance is solubility, especially aqueous solubility [8] . A drug must possess some aqueous solubility for therapeutic efficacy in the physiological pH range of 1 to 8.

Table 2.1:IP Index

Descriptive term	Parts of solvent required for Parts of soluble
Very soluble	Less than 1
Freely soluble	From 1to 10
Soluble	From 10 to 30
Sparingly soluble	From 30to 100
slightly soluble	From 100 to1000
Very slightly soluble	From 1000 to 10000
Practically insoluble	10000 or more

For the determination of solubility of Canagliflozin in various solvents that were methanol, ethanol, chloroform and distilled water etc. 5mg of Canagliflozin was added to 10 ml of each solvent in a test tube and shaken for few minutes at room temperature (21.0 ± 1.5°C).

2.2.3 Loss on drying (%)

Loss on drying is the loss of weight expressed as percentage w/w resulting from water and volatile matter of any kind that can be driven off under specified conditions[9] .

Loss on drying was directly measured by IR moisture balance. Firstly calibrated the

instrument by knob, then taken 5 gram of sample (powder) and fixed the temperature at 100°C to 105°C for 15 minutes and constant reading, and fixed the knob and check percent moisture.

$$\text{Loss on drying (\%)} = \frac{\text{initial weight of sample - weight of sample after drying x 100}}{\text{Initial weight of sample}}$$

2.2.4 Melting point

Melting point of Canagliflozin was determined using open capillary method by melting point apparatus. Fine powder of the drug was filled in glass capillary tube which was sealed at one end. The capillary tube was tied to the thermometer and thermometer was kept in theils tube apparatus and then slowly increased the temperature of the apparatus and recorded the temperature at which drug was completely melted [10] . The observed melting point of the drug was compared with melting point given in literature.

2.2.5 Determination of UV-visible absorption maxima of Canagliflozin: Preparation of standard solutions

A standard stock solution of Canagliflozin was prepared by dissolving 10 mg (accurately weighed) of the standard Canagliflozin in 10 ml of methanol. This stock solution was further diluted to get working standard solutions of 10µg/ml. Aliquots (0.05, 0.1, 0.15, 0.2, 0.25ml) of working standard solution were transferred into a series of 10 ml volumetric flasks to get the desired concentration range for calibration curve. The volumes were made up with phosphate buffer pH 7.4.

2.2.6 FTIR spectroscopy of Canagliflozin:

The purity of pure drug was determined by I.R. Approximately 10 mg of Canagliflozin was triturated with 100 mg of dried potassium bromide (KBr) in agatte mortar. Pellet was prepared by using KBr press pellet method [81] . Pellet was scanned between the ranges of 400 to 2000 cm-1 with background correction. The spectrum was recorded and major peaks were determined.

2.3 Development of transdermal patches

A) Preparation of blank patches:

Accurately weighed polymers taken in combination and dissolved in respective solvent (chloroform and methanol in the ratio of 1:1 v/v) then poured in petridish with glycerin on plain surface. Then film was dry over night at room temperature.

B) Preparation of rate controlling membrane

Eudragit RLPO and RSPO were used for the preparation of rate controlling membranes. Polymers were dissolved in chloroform and methanol with PEG 600 as plasticizer. Then solution was then poured into a glass Petri dish. The solvent was allowed to evaporate under room temperature for 24 hrs[11] .

C) Preparation of matrix type transdermal patches

Transdermal patches composed of different polymers HPMC, Ethyl Cellulose, Eudragit RLPO and Eudragit RSPO [12] . The polymers were dissolved in chloroform and methanol along with plasticizer. Then the solution was poured into a glass Petri dish containing Glycerin. The solvent was allowed to evaporate under room temperature for 24 hrs. The polymers (total weight: 500 mg) and drug (20 mg) were weighed in requisite ratios and dissolved in 10 ml of chloroform and methanol and PEG 400. After vortex then the solution was poured on glycerin placed in a glass Petri dish and driedat room temperature for 24 hrs[13] .

RESULTS AND DISCUSSION

3.1 Preformulation study

3.1.1 Organoleptic properties:

Table 3: Organoleptic characteristics of Canagliflozin

S. No.	Properties studied	Results
1.	Colour	White
2.	Odour	Odorless
3.	Taste	Bitter
4.	Appearance/Morphology	Fine powder

3.1.2 Solubility analysis:

Table 3.1: Solubility determination of Canagliflozin in various solvent

Solvents	Results of Solubility
Methanol	Soluble
Ethanol	Soluble
Chloroform	Sparingly soluble
Distilled water	Sparingly soluble
Phosphate buffer 7.4 pH	Sparingly soluble
0.1 N HCl	Sparingly soluble
0.1 N NaOH	Sparingly soluble

It was found that Canagliflozin was soluble in ethanol and methanol, sparingly soluble in phosphate buffer 7.4 pH, 0.1 N HCl, distilled water, chloroform and 0.1 NNaOH.

3.1.3 Results of loss on drying

Results:

Results of loss on drying of Canagliflozin was found 0.147±0.004%. 3.1.3

Melting point Results:

The melting point of Canagliflozin was found to be 70-72°C.

3.1.4 Determination of UV-visible absorption maxima of Canagliflozin

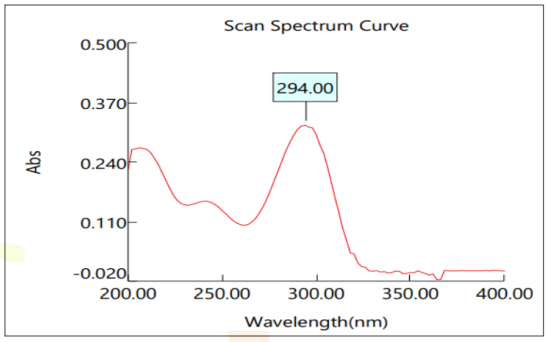

Figure 3: Determination of λmax of Canagliflozin

Table 7.3: Calibration curve of Canagliflozin

S. No.	Concentration (µg/ml)	Mean Absorbance
1	0	0
2	5	0.151±0.005
3	10	0.321±0.003
4	15	0.474±0.001
5	20	0.632±0.002
6	25	0.778±0.004

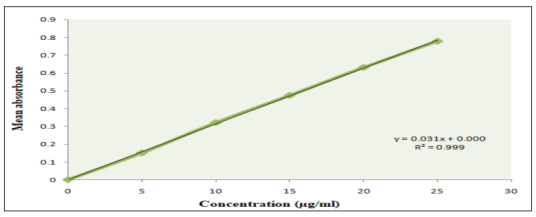

Figure 3.1: Calibration curve of Canagliflozin

3.1.5 FTIR spectroscopy of Canagliflozin

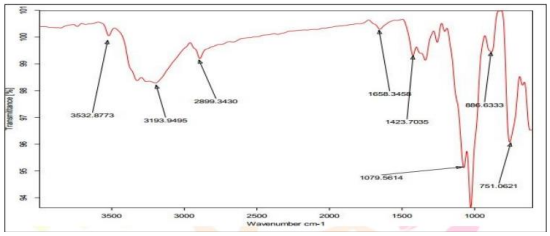

Figure 3.2: IR spectra of Sample Canagliflozin

3.2 Evaluation of Formulated Patch

3.2.1 Thickness:

The thickness of the films varied from 85±5 to 96±3 mm. The values obtained for allthe formulations are given in the table 3

3.2.2 Folding Endurance:

The folding endurance was measured in triplicate, according to procedure given in table 5.5 and the folding endurance was found to be in the range. The thickness was approximately close to every formulation. It depends on polymer ratio. All the patches showed satisfactory folding endurance properties. Folding endurance values of all formulation more than 185 indicating good elasticity and strength.

Table 3 : Thicknesses and folding endurance of different formulations

S. No.	Formulation Code	Thickness* (µm)	Folding Endurance* (Times)
1.	F1	98±5	168±5
2.	F2	100±7	175±7
3.	F3	102±9	205±6
4.	F4	95±8	185±8
5.	F5	98±4	174±4
6.	F6	110±6	165±3

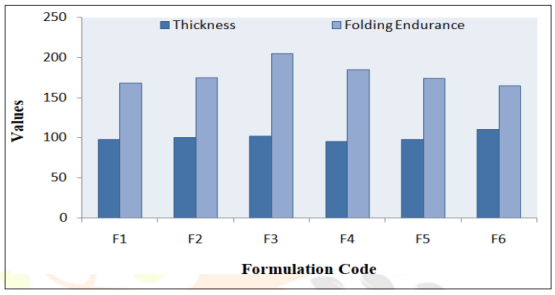

Figure 3.3: Graph of thickness and folding endurance

3.2.3 Moisture Content:

The moisture content was determined by keeping patches in a desiccators containing activated silica. The percentage moisture uptake was calculated as the difference between initial and final weight with respect to final weight. The results of the moisture content studies for different formulations are shown in Table 3.1

3.2.4 Moisture Uptake:

The percentage moisture uptake was calculated as the difference between final andinitial weight with respect to initial weight. The results of moisture uptake studies for different formulations are shown in Table 3.1 The formulation F3 show lowest moisture content and moisture uptake than other formulation. This is due to because of polymer ratio (like Ethyl Cellulose). If lower moisture content in transdermal patch it be good to prevent the brittleness with 100% dryness and also maintain the stability of formulation. If formulation content higher moisture it can lead the microbial contamination during the storage of patchs.

Table 3.1: % Moisture content and moisture uptake of different formulation

S. No.	Formulation Code	% Moisture content*	% Moisture uptake*
1.	F1	6.98±0.25	3.45±0.33
2.	F2	7.02±0.35	3.65±0.65
3.	F3	5.68±0.24	1.95±0.25
4.	F4	7.85±0.15	4.25±0.14
5.	F5	6.45±0.32	3.69±0.25
6.	F6	6.85±0.14	3.47±0.21

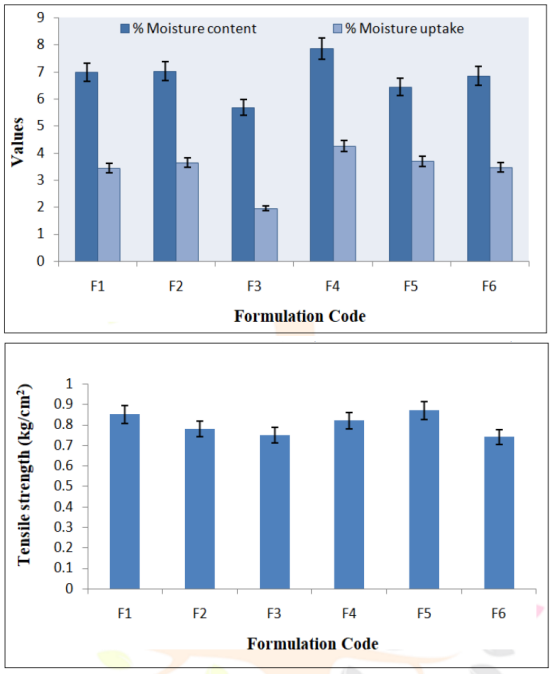

Figure 3.5: Graph of Tensile strength of different formulation

The prepared patch showed good tensile strength and there was no cracking sign inpatch. There was an increase in tensile strength with an increase in Eudragit RLPOin polymers ratio.

3.2.5 Drug Content Analysis:

The drug content analysis of different formulations was done. The drug content ranged between 98.45±0.65 and 99.45±032. The percentage drug content of all formulations is shown in Table 3.3.

Table 3.3: Percentage drug content of all the formulations

S. No	Formulation Code	% Drug content
1	F1	97.78±0.45
2	F2	96.85±0.25
3	F3	99.12±0.36
4	F4	97.78±0.21
5	F5	98.85±0.18
6	F6	98.47±0.25

*Average of Three determinations (n=3, Mean ± S.D.)

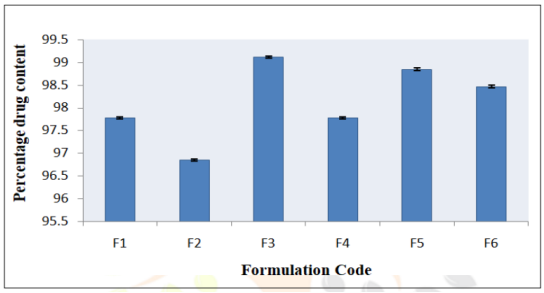

Figure 3.6: Graph of percentage drug content of formulation F1 to F6

This test is essential to check the uniformity of drug content in different patches from a single batch. The drug content analysis of patch show that the process employed to prepared patch was capable of giving uniformity drug content and minimum batch variability. F3 is optimized formulation that shows the good result.

3.2.1 In-vitro permeation studies:

The in vitro permeation studies are prediction of in vivo performance of a drug. These studies were performed for different formulations across egg membrane usingphosphate buffer, pH 7.4 as an in vitro study fluid in the receptor compartment of Franz diffusion cell. The results of these studies are given in Tables 3.4-3.6 and Fig. 3.7-3.9.

Table 3.4: In Vitro % permeation profile of Canagliflozin in formulation F1-F6

Time	% of Drug Release						
(hr)	F1	F2	F3	F4	F5	F6	Pure Drug
0.5	43.25	35.65	28.85	38.85	35.45	30.25	55.85
1	55.65	48.85	36.65	49.98	45.65	42.25	78.85
2	69.98	59.98	48.89	62.23	59.98	55.65	98.78
4	78.85	69.98	65.56	78.85	74.45	69.98	-
6	89.98	79.98	73.32	85.45	82.23	79.85	-
8	99.45	93.32	82.23	92.23	95.65	88.85	-
10	99.85	98.85	93.36	98.85	98.78	98.85	-
12	99.92	99.12	99.74	99.05	99.12	99.15	-

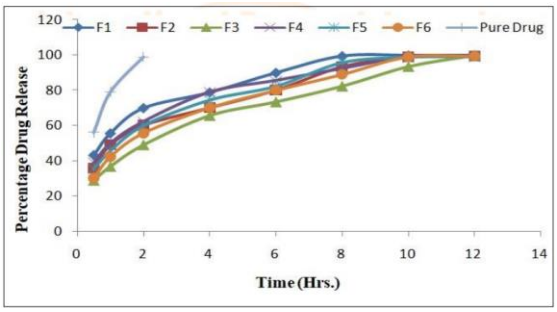

Figure 3.7: % of Drug release of Canagliflozin transdermal patches

3.2.1.1 Release kinetics of Canagliflozin Transdermal patches

Table 3.5: In-vitro drug release data for optimized formulation F3

Time (h)	Square Root Time (h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	28.85	1.460	71.15	1.852
1	1	0	36.65	1.564	63.35	1.802
2	1.414	0.301	48.89	1.689	51.11	1.709
4	2	0.602	65.56	1.817	34.44	1.537
6	2.449	0.778	73.32	1.865	26.68	1.426
8	2.828	0.903	82.23	1.915	17.77	1.250
10	3.162	1	93.36	1.970	6.64	0.822
12	3.464	1.079	99.74	1.999	0.26	-0.585

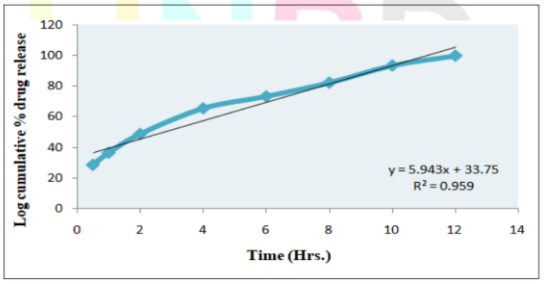

Figure 3.8: Cumulative % drug released Vs Time

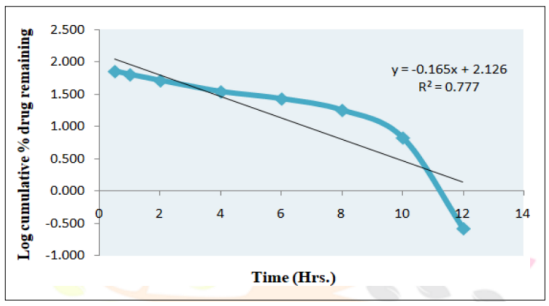

Figure 3.9: Log cumulative % drug remaining Vs Time

Table 3.6: Regression analysis data of Canagliflozin transdermal patches

Batch	Zero Order	First Order
	R^2	
F3	0. 959	0. 777

The In-vitro permeation study was done to see the effect of polymers through the Franz diffusion cell from patch having Eudragit RLPO, RSPO, HPMC, EC in different conc. to optimized formulation for in-vitro study. All the formulation was studied and all data fitted on Zero Order, First Order to explain the diffusionmechanism and pattern.

The % cumulative drug release was calculated over the study time range in 0-12 hrs.Data analysis for order of release kinetics the formulation followed zero order release kinetics. From the in-vitro permeation study it was confirmed that the releaseof formulation F3 was to be found higher as compared to other formulation (F1, F2, F4, F5, F6).

4. SUMMARY AND CONCLUSION:

Transdermal route has gained accolade as it has several advantages over conventional forms such as, avoids first pass metabolism and lowers gastrointestinal irritation that are associated with oral administration. Easy termination of therapy enables a constant plasma level profile that results in decreased side effects are some other advantages. The release of the drugs from topical preparations depends on the physicochemical properties of the drug and gels employed. Gels for dermatological use have many advantageous properties such as thixotropic, emollient, greaseless, easily spreadable, and easily removable. Gelling agents when mixed with appropriate solvent entangle to form a three-dimensional colloidal network that limits fluid flow by entrapment and immobilization of the solvent molecules. One more advantage of network structure of gels is their resistance to deformation and hence its viscoelastic properties.

In the current research was planned to formulate and evaluate transdermal patch containing Canagliflozin using HPMC, RLPO, RSPO, EC and PEG. The prepared gels were evaluated for clarity, viscosity, drug content and in vitro permeation studies.

The thickness of the films varied from 98±5 to 110±6mm. The thickness was approximately close to every formulation. It depends on polymer ratio. All the patches showed satisfactory folding endurance properties. Folding endurance values of all formulation more than 205±6 indicating good elasticity and strength.

The moisture content was determined by keeping patches in a desiccators containing activated silica. The percentage moisture uptake was calculated as the difference between initial and final weight with respect to final weight.

The formulation F3 show lowest moisture content and moisture uptake than other formulation. This is due to because of polymer ratio (like Ethyl Cellulose). If lower moisture content in transdermal patch it be good to prevent the brittleness with 100% dryness and also maintain the

stability of formulation. If formulation content higher moisture it can lead the microbial contamination during the storage of patchs.The tensile strength was found to be in the range of 0.74±0.02 to 0.87±0.03. The formulation Canagliflozin F3 showed the best tensile strength.

The prepared patch showed good tensile strength and there was no cracking sign inpatch. There was an increase in tensile strength with an increase in Eudragit RLPO in polymers ratio. The drug content ranged between 97.78±0.45 and 99.12±0.36.

This test is essential to check the uniformity of drug content in different patchesfrom a single batch. The drug content analysis of patch show that the processemployed to prepared patch was capable of giving uniformity drug content and minimum batch variability. F3 is optimized formulation that shows the good result. The In-vitro permeation study was done to see the effect of polymers through theFranz diffusion cell from patch having Eudragit RLPO, RSPO, HPMC, EC indifferent conc. to optimized formulation for in-vitro study. All the formulation wasstudied and all data fitted on Zero Order, First Order to explain the diffusion mechanism and pattern.

The % cumulative drug release was calculated over the study time range in 0-12 hrs.Data analysis for order of release kinetics the formulation followed zero order release kinetics. From the in-vitro permeation study it was confirmed that the releaseof formulation F3 was to be found higher as compared to other formulation (F1, F2, F4, F5, F6).

4.1 CONCLUSION:

An attempt was made in the current study to administer canagliflozin, a new anti-hypertensive medication, transdermally as transdermal patches. Transdermal matrix patches were created, and it was discovered that this particular matrix type of patch worked well. The optimal matrix type formulation, F3, which includes Eudragit RLPO and HPMC, was chosen from among the several formulations (F1 to F6). It was also discovered that the drug permeation profile followed zero order kinetics. The patches were translucent, pliable, and thin. The results of this investigation demonstrated that canagliflozin matrix transdermal patches performed better in vitro than the medication alone.

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