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DEVELOPMENT AND CHARACTERIZATION OF TRANSDERMAL DRUG DELIVERY FOR ENHANCEMENT OF BIOAVAILABILITY OF LINAGLIPTIN

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Abstract:
Diabetes mellitus is a serious and spreading health issue that is a significant contributor to early death and chronic illness. It is a long-term metabolic condition defined by chronic insulin resistance and high blood glucose levels (hyperglycemia) brought on by insulin insufficiency. Linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, is frequently prescribed to treat type 2 diabetes. Although Linagliptin has a low bioavailability (30%) due to its poor penetration profile and low water solubility. Furthermore, the requirement to maintain stable plasma concentrations for efficient long-term blood sugar control in diabetic patients supports the need for transdermal delivery of linagliptin. Transdermal matrix patches were created, and it was determined that the matrix kind of patches were suitable. The optimal formulation of the various matrix types (F1 to F6) was decided to be F5, which contains Eudragit RSPO and HPMC. It was also discovered that the drug permeation profile followed zero order kinetics. The patches were translucent, thin, and flexible. The current investigation revealed that Linagliptin matrix transdermal patches performed better in vitro than pure medication.

Key words: *Diabetes mellitus, Linagliptin, Transdermal matrix patches, Formulation, Evaluation.*

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INTRODUCTION:

Transdermal drug delivery system is the system in which the delivery of the active ingredients of a drug occurs penetrate through the skin. This system is designed to improve the therapeutic efficacy and safety of the drugs because drug delivered through the skin at a predetermined and controlled rate.

In recent years, the use of a number of biophysical techniques has aided in our understanding of the nature of the stratum corneum barrier and the way in which chemicals interact with and influence this structure. A better understanding of the interaction of enhancers with the stratum corneum and the development of structure activity relationships for enhancers will aid in the design of enhancers with optimal characteristics and minimal toxicity.

In order to increase the range of drugs available for transdermal delivery the use of physical enhancement techniques have been developed in an attempt to compromise skin barrier function in a reversible manner without concomitant skin irritation. Several alternative physical methods have emerged to transiently break the stratumcorneum barrier1-3.
The skin, as the largest organ of the body, account for more than 10% of body mass and receives about one third of the blood circulating through the body, serves as a protective layer of the underlying tissues such as muscles, ligaments and internal organs, shielding it from exogenous molecules as well as from mechanical and radiation-induced injuries. The skin also plays a role in immunology and metabolism, regulates body temperature, serves as an excretory organ through sebaceous and sweat glands andcontains sensory nerve endings for the perception of touch, temperature, pain and pressure. The skin varies in color, thickness and presence of nails, hairs and glands between the different regions of the body, although all types of skin have the same basic structure4-5.

Transdermal drug delivery system (TDDS) has been an increased interest in the drug administration via the skin for both local therapeutic effects on diseased skin (topical delivery) as well as for systemic delivery of drugs. The skin as a site of drug delivery has a number of significant advantages over many other routes of drug administration, including the ability to avoid problems of gastric irritation, pH and emptying rate effects, avoid hepatic first-pass metabolism thereby increasing the bioavailability of drug, reduce the risk of systemic side effects by minimizing plasma concentrations compared to oral therapy, provide a sustained release of drug at the site of application; rapid termination of therapy by removal of the device or formulation, the reduction of fluctuations in plasma levels of drugs, and avoid pain associated with injections. The transdermal delivery can also eliminate pulsed entry into the systemic circulation, which might often cause undesirable side effects.

Diabetes mellitus is a major and growing health problem worldwide and an important cause of prolonged ill health and early death. It is a chronic metabolic disorder characterized by a high blood glucose concentration (hyperglycemia) caused by insulin deficiency, and it is often combined with insulin resistance.

Linagliptin, dipeptidyl peptidase-4 (DPP-4) inhibitor, widely used in the treatment of diabetes mellitus type 2. Though, low aqueous solubility and poor permeation profile of Linagliptin results in the low bioavailability (~30%). The need for transdermal delivery of Linagliptin is further justified due to the requirement of maintaining unfluctuating plasma concentrations for effective management of blood sugar for long period in diabetic patients.

Material and Methods:

Preparation of matrix type transdermal patches:

Transdermal patches composed of different polymers HPMC, Ethyl Cellulose, Eudragit RLPO and Eudragit RSPO6. 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 (5 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 dried at room temperature for 24 hrs.

Table 1: Preparation of matrix type transdermal patches

Formulation Code	Drug (mg)	HPMC (mg)	RLPO (mg)	RSPO (mg)	Ethyl cellulose (mg)	Total polymer weight (mg)	Plasticizer % w/w of total polymer PEG 6000 (ml)	Permeation Enhancer % w/w of total polymer (Methanol, chloroform) ml
F1	60	350	50	-	100	500	0.5	10
F2	60	400	50	-	50	500	0.5	10
F3	60	450	50	-	0	500	0.5	10
F4	60	350	-	50	100	500	0.5	10
F5	60	400	-	50	50	500	0.5	10
F6	60	450	-	50	0	500	0.5	10

Dose calculations:

- Width of the plate = 5cm
- Length of the plate = 12cm
- No. of 2.5 x 2.5 cm2 wafers present whole plate = 12
- Each wafers contains 5 mg of drug.
- 12 no. of wafers contains mg of drug? = 5×12 = 60mg
- The amount of drug added in each plate was approximately equal to 60mg.

Evaluation parameters:

The prepared transdermal films were evaluated for the following parameters:

Microscopic evaluation

An optical microscope (Olympus-Cover-018) with a camera attachment (Minolta) was used to observe the shape of the prepared Transdermal patch for all formulation.

Thickness

The thickness of films was measured by Vernier calipers.The thickness of patches were measured at three different places and average of three readings was taken with standard deviation7.

Folding endurance

This was determined by repeatedly folding one film at the same place until it broken. The number of times the film could be folded at the same place without breaking / cracking gave the value of folding endurance8.

Tensile strength.

Cut the patch at the centre having 2cm length and 2cm breadth. Patch was hanged on top and lower side of instrument, then start the switch and note the reading on screen. The thickness and breadth of strips were noted at three sites and average value was taken for calculation9.

$$Tensile\ strength\ (s) = \frac{Applied\ Force}{Cross\ section\ area}$$

Where, S = tensile stress in 980 dynes/cm2
m = mass in grams
g = acceleration due to gravity (980 dynes/cm2)
b = breadth of strip in centimeters
t = thickness of strip in centimeters

Percentage of moisture content

The prepared patches were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs10. Individual films were weighed. The percentage of moisture content was calculated as the difference between final and initial weight with respect to initial weight.

Percentage of moisture uptake

Firstly weighed the patches and then kept in a desiccators at room temperature for 24 hrs and then its exposed to 84% RH (A saturated solution of potassium chloride) in a desiccators. The % of moisture uptake was calculated by difference between final and initial weight with respect to initial weight.

Drug content analysis

The patches (n = 3) of specified area (6.16cm2) were taken into a 10 ml volumetric flask and dissolved in methanol (10ml) with the help of shaker. After the vortex the solution was filtered and prepared subsequent dilutions and analyzed by UV spectrophotometer at 276 nm11.

***In vitro* skin permeation study:**

The in vitro skin permeation study was done by using a Franz diffusion cell (receptor compartment

capacity: 80 ml: surface area: 3.14 cm2. The egg membrane was separated and used for in vitro study. The receiver compartment was filled with 40 ml of phosphate buffer, pH 7.4. The Transdermal patch was firmly pressed onto the centre of the egg membrane and then the membrane was mounted on the donor compartment12. The donor compartment was then placed in position such that the surface of membrane just touches the receptor fluid surface. The whole assembly was kept on a magnetic stirrer with suitable rpm throughout the experiment using magnetic beads. The temperature of receptor compartment was maintained at 37± 0.5ºC.

The samples were withdrawn at different time intervals up to 10 hrs and analyzed for drug content. Receptor phase was replaced with an equal volume of buffer solution at each time interval.

RESULTS AND DISCUSSION:

In the current research was planned to formulate and evaluate transdermal patch containing Linagliptin using HPMC, RLPO, RSPO, EC and PEG. The preparedgels were evaluated for clarity, viscosity, drug content and *in vitro* permeation studies. The thickness of the films varied from 88±3 to 97±4mm. The folding endurance was measured in triplicate, according to standard procedure 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±5 indicating good elasticity and strength.The formulation F5 show lowest moisture content and moisture uptake than other formulation. This is due to because of polymer ratio (HPMC, RSPO and 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 0.63 to 0.76. The formulation Linagliptin F5 showed the comparable tensile strength. The prepared patch showed good tensile strength and there was no cracking sign in patch. There was an increase in tensile strength with an increase in HPMC in polymers ratio. The drug content analysis of different formulations was done. The drug content ranged between 98.45±0.65 and 99.45±032. 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. F5 is optimized formulation that shows the good result.

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 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 release of formulation F5 was to be found higher as compared to other formulation (F1, F2, F4, F5, F6).

Table 2: Thicknesses and folding endurance of different formulations

Formulation Code	Thickness* (µm)	Folding Endurance* (Times)	% Moisture content*	% Moisture uptake*	Tensile strength (kg/cm^2)	% Drug content
F1	88±3	142±6	6.65±0.25	3.45±0.32	0.63	98.85±0.25
F2	92±2	146±5	6.32±0.36	3.12±0.25	0.68	98.45±0.65
F3	97±4	158±5	6.54±0.45	3.26±0.14	0.72	99.45±032
F4	89±5	160±6	6.32±0.36	3.65±0.26	0.69	98.85±0.21
F5	93±2	185±5	5.85±0.25	2.85±0.32	0.65	98.96±0.45
F6	97±3	135±3	6.05±0.21	3.14±0.25	0.76	99.05±0.25

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

Table 3: *In-vitro* drug release data for optimized formulation F5

Time (h)	Square Root of 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	22.12	1.345	77.88	1.891
1	1	0	38.85	1.589	61.15	1.786
2	1.414	0.301	49.95	1.699	50.05	1.699
4	2	0.602	58.78	1.769	41.22	1.615
6	2.449	0.778	63.32	1.802	36.68	1.564
8	2.828	0.903	75.45	1.878	24.55	1.390
10	3.162	1	86.65	1.938	13.35	1.125
12	3.464	1.079	98.45	1.993	1.55	0.190

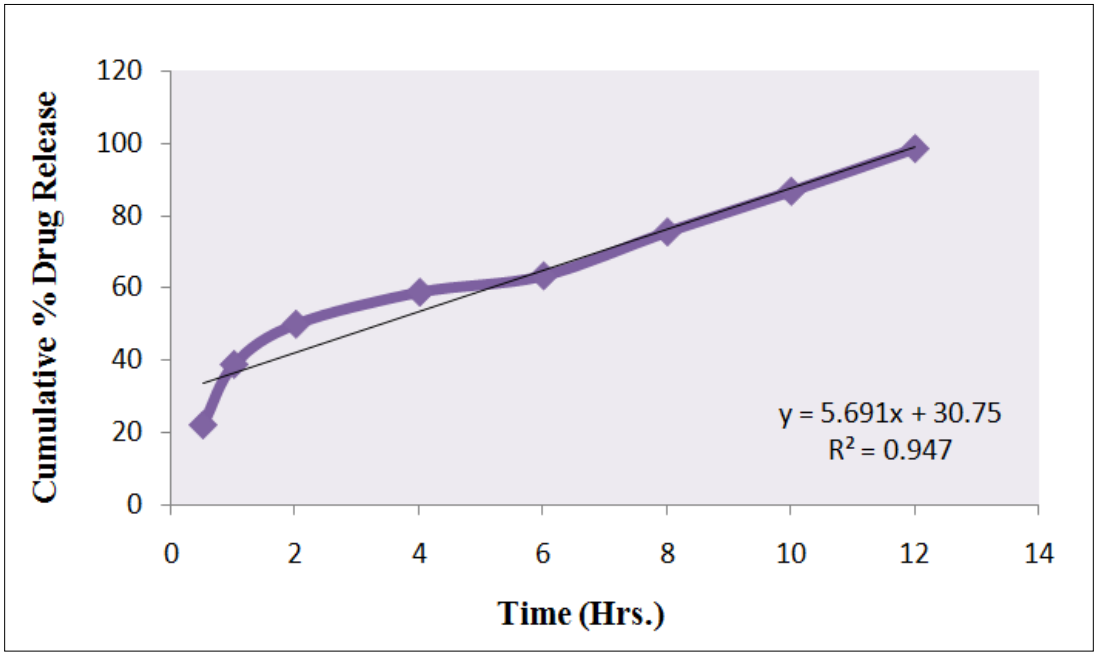

Figure 1: Cumulative % drug released Vs Time

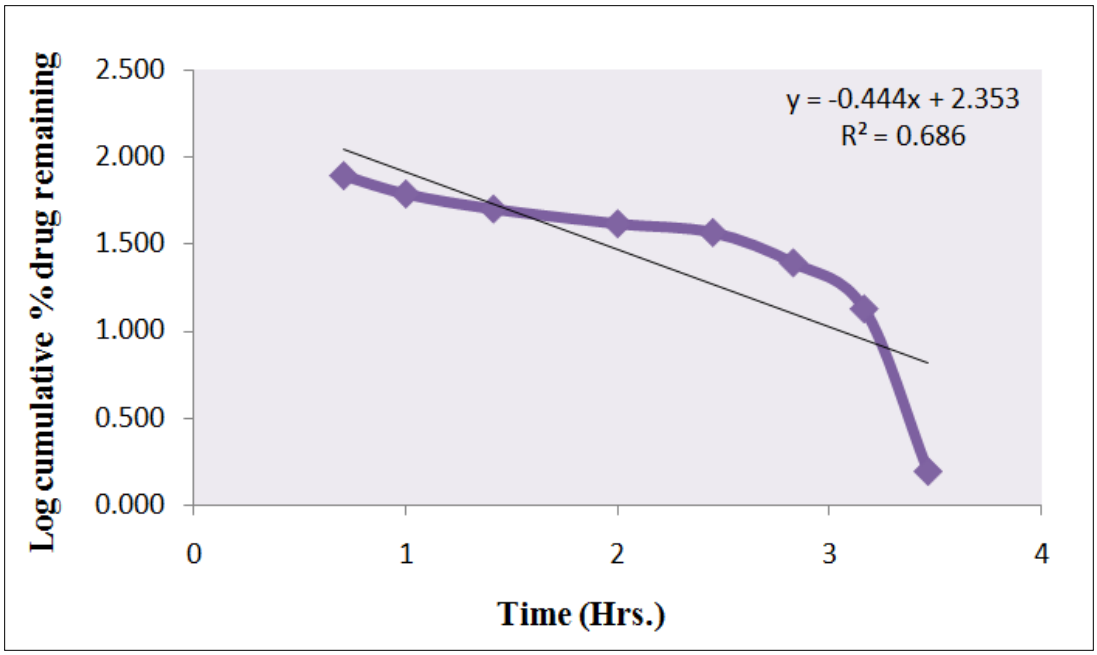

Figure 2: Log cumulative % drug remaining Vs Time

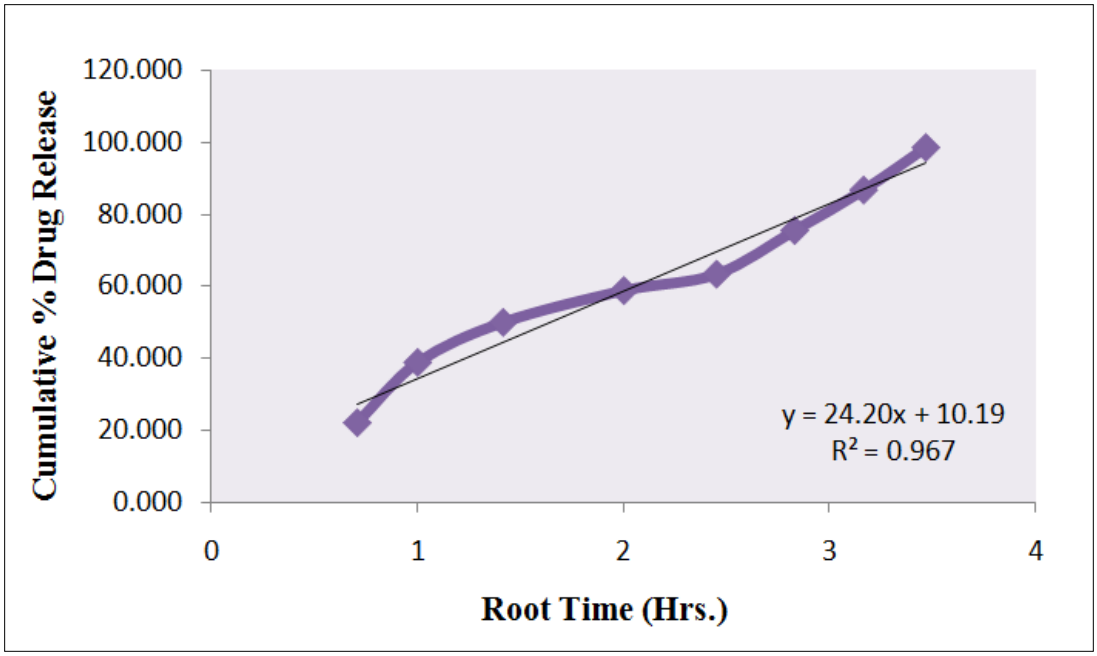

Figure 3: Cumulative % drug release Vs Root Time

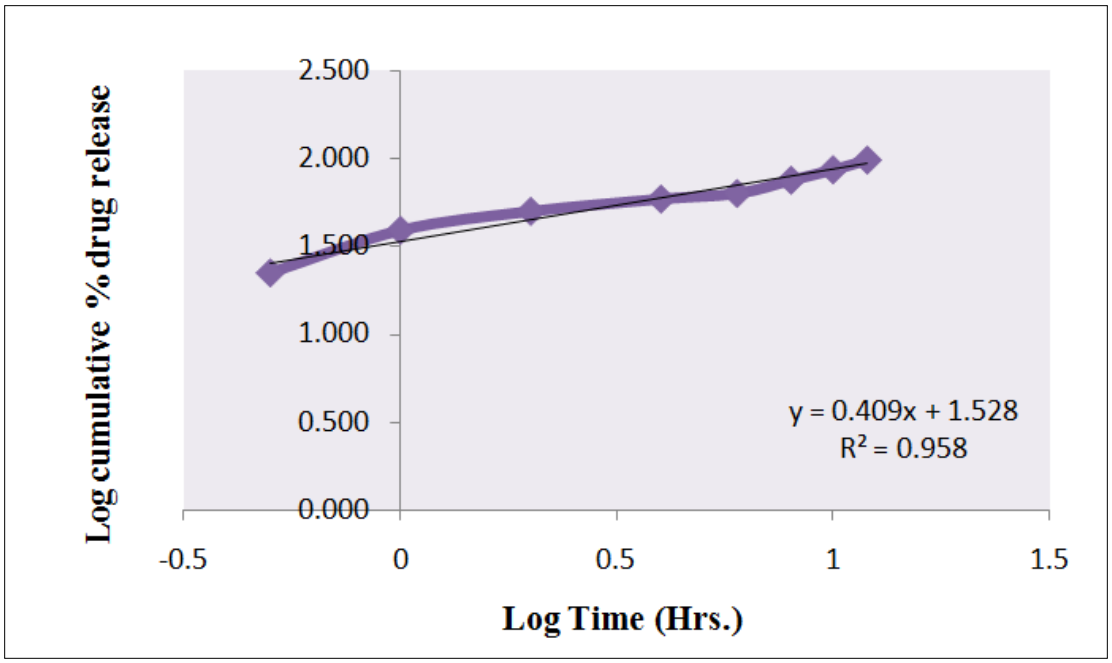

Figure 4: Log Cumulative % drug release Vs Log Time

Table 4: Regression analysis data of Linagliptin transdermal patches

Batch	Zero Order	First Order	Higuchi	Korsmeyer peppas
	R^2			
F5	0.947	0.686	0.967	0.958

CONCLUSION:

In the present study, an attempt was made to deliver a novel anti diabetic drug, Linagliptin through Transdermal route in the form of Transdermal patches. Transdermal patches of matrix were prepared out of which matrix type of patches was found to be satisfactory. Among the different formulations of matrix type (F1 to F6); the formulation F5 containing Eudragit RSPO and HPMC was selected as best formulation. The drug permeation profile was also found to follow zero order kinetics. The patches were thin, flexible and transparent. The Present study showed that matrix Transdermal patches of Linagliptin exhibited better *in vitro* performance than pure drug.

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