Research Article

Formulation Development and *In-Vitro* Evaluation of Linagliptin Transdermal Patch Using Permeability Enhancer

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ABSTRACT

Diabetes is a serious and widespread health problem and major reason early deaths and serious persistent (chronic) disease. It is a long-standing metabolic disease characterized by chronic insulin resistance and hyperglycemia caused by insufficient insulin. Linagliptin is dipeptidyl peptidase-4 inhibitor (DPP-4 inhibitor) which is often prescribed to treat the type II diabetes. But, linagliptin has a poor permeability property and little water solubility, and this is the reason linagliptin have a low Bioavailability which is 29.5%. Furthermore, the need to maintain stable plasma concentrations for efficient long-lasting control of glycemic level in diabetic patients supports the need for transdermal administration of linagliptin. TDDS utilised to deliver drugs into the systemic circulation through intact skin. It is an alternative to subcutaneous injections and oral drug delivery systems. The major aim of this present research work is the formulation of a linagliptin transdermal patch using suitable polymers and permeation enhancer, which aims to increase of the bioavailability of poorly water-soluble drug by permeating the skin surface and it also makes it possible to avoid the hepatic first-pass metabolism. A transdermal matrix patch was made and found to be suitable. Utilising Box-responsive Behnken's surface design, the formulation was improved. According to the Design of Experiment, fifteen formulations was total developed and examined for folding endurance and in-vitro drug release. Linagliptin patches' ideal patch level was determined by software using folding resistance and drug release in in-vitro. In line with expectations, from the fifteen formulations the most improved patch which was H5 that release 64.78 percent of the drug throughout the course of 24 hours. Based on the findings this is can be concluded that the patch prepared by HPMC K100, Eudragit L100, PEG-400 and Menthol and loaded with linagliptin can be effectively treat the Diabetes.

Keywords: Transdermal Patch, Linagliptin, Permeability Enhancer.

INTRODUCTION

One of the drugs presently being developed for treatment of Hyperglycemic state in type II diabetes mellitus, the name of the drug is linagliptin, which is DPP-4 inhibitors. All drugs in this class function by blocking the DPP-4 enzyme, despite structural differences between them. These substances prolong the half-life of the incretin hormones that increases production of insulin and does so in a dependent of glucose manner. They are also preventing glucagon storage in a glucose-dependent manner.[1] According to Richter, Bandeira- Echtler, Bergerhoff, and Lerch (2008), this medication class's glucose-dependent mode of action carries a relatively reduced risk of hypoglycemia episodes than other antidiabetic drugs. In comparison to previously marketed DPP- 4 impediments, Linagliptin (LNG) has different pharmacokinetic (PK) characteristics, which may have some advantages or benefits in therapeutic practice. On May 2, 2011, the USFDA approved this medication to treat the patients with type II diabetes.[2-3]

The patients which have type II diabetes administered five mg of the linagliptin orally per day once. According to, this medicine has a maximum plasma concentration of 8.9 nmol/l after 1.5 hours the administration of 5 mg drug dose and half-life of excretion is 69.7 hours.[4-5] This medicine has a 30% oral bioavailability, the enterohepatic route accounts for the majority of its excretion and less than 7% of renal elimination, according to Aletti and Cheng-Lai,2012 and A.J. Scheen,2010.

One of the key benefits of this medication is that patients have hepatic or renal impairment do not need to modify their dosage because linagliptin is firstly excreted unaltered by the entero-hepatic system.[6] Additionally, it was demonstrated in-vitro and in-vivo that linagliptin's mechanism, duration of action, potency, and selectivity were superior to those who are currently other DPP-4 inhibitors present in the market.[7]

Parenteral route is the II most prevalent method of medications delivery, with oral route administration accounting for around 80% of all medications. But common issues with oral medication administration include pH variations, enzymatic activity, adverse effects, varying transit times, and drug degradation by first-pass metabolism.[8]

Medications are the utilised topical on skin in the form of patches that released through the skin at a restrained and planned amount for systemic action in TDDS. This method of transdermal drug delivery is well-liked for local (Therapeutic effect in sick skin) and systemic drug delivery.

The transdermal method offers continuous distribution of medications with brief biological half-lives, prevents pulsatile drug entry into the blood circulation (eliminating unwanted side effects), and most crucially, offers

continual and control assurances of accurate medication delivery.[9] Compared to many other medication delivery methods, transdermal drug administration systems provide a number of significant advantages. This includes gastrointestinal discomfort, the consequences of altered pH and stomach emptying rates, and hepatic first pass metabolism, which increases medication bioavailability. When comparison is done to oral medicine delivery, this method lowers the drug's plasma concentration, provides sustained drug release at the site of administration, facilitates quick therapy termination by removing the formulation or device, and avoids the possibility of systemic side effects.

TDDS (TRANSDERMAL DRUG DELIVERY SYSTEM)[10-11]

The words "transdermal" and "trans" (meaning through, across, or skin) were combined to create this term. To address the issues with oral or parenteral routes, the transdermal drug delivery system was created. Patients can administer their own medications in a comfortable, painless manner thanks to transdermal technology. TDDS are characterised as dosage forms that distribute medications systemically via skin for the pre-defined duration of time at a controlled pace.

Skin as a Site for Transdermal Technology[12-13]

Skin is the largest organ of the human body. A permeable barrier to transdermal (TD) absorption that can be used to treat a variety of biological and chemical substances. Medication penetration and absorption through the dermis are two medication delivery methods that are significantly influenced by the skin.

Skin Role

- Defend against physical, chemical and microbial attack.
- Prevents UV rays to penetrating.
- It controls the blood pressure (BP).

Human skin structure:

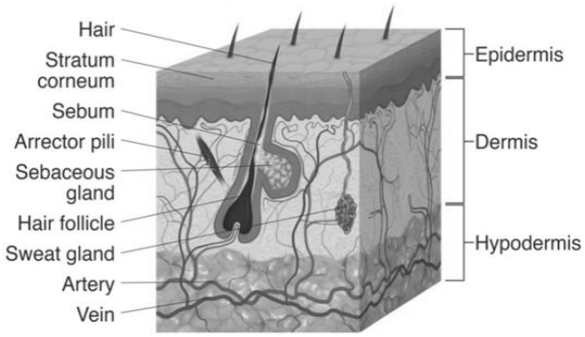

Figure 1: Human skin structure

It is further more divided into 3 layers

- Epidermis
- Dermis
- Hypodermis

Epidermis

Epidermis is the outer most layer of the skin, is reasonably fine and resilient. Keratinocytes make up the epidermis' outer layer. The epidermal surface is slowly being migrated up by fresh keratinocytes. It has a thickness of 100 m. The main factor preventing diffusions and penetrations through the skin is subcutaneous. The epidermis has 5 layers.

- Stratum basal
- Spinosum
- Granulosum
- Lucidum
- Corneum

Dermis

Despite having numerous blood arteries, lymphatics, and nerve terminals, the dermis is often elastic. Arterioles and venules in the dermis branch out in a broad horizontal pattern that drains capillaries to the sweat and hair glands and generates nerve plexuses. This huge network of cutaneous ducts connects the important circulations. Antigens are extracted from clear liquid substances by skin capillaries.

Hypodermis

The tissue of the hypodermis supports the dermis and epidermis, two of the top and inner layers of the skin. It ought to serve as a fat reserve. The subcutaneous layer offers nutrients, physical protection, and aids in controlling body temperature. Additionally, it may carry vessels of blood and nerves endings which reach to the skin and pressure – sensing organs. TDDS necessitates the medication cross through every layer in order to generate the required current, as opposed to topical drug delivery which only needs drug dispersion through the SC and medication retention in skin layers.

Transdermal Patch[14]

Skin patch is another name of the transdermal patch which is an adhesive patch that can apply on the skin which contain drugs that is used to be absorbed into systemic circulation through by the skin.

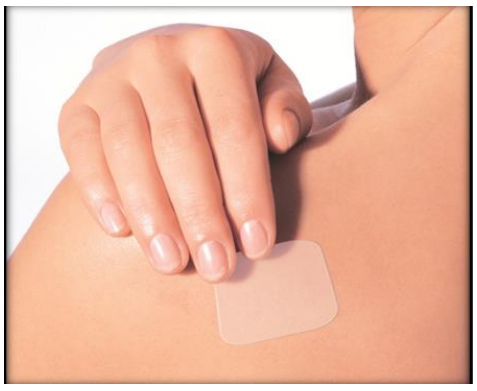

Figure 2: Transdermal Patch

Advantage of transdermal patches

- Patch is non-invasive and pain avoidable approach to provide medicine to body.
- Drugs that are significantly destroyed in the liver, ineffectively absorption from gut and dissolution by stomach acids can be administered more effectively via topical patches.
- Topical patches that provide drugs in a control, regular rate over extended periods of time.
- Topical patches are less harmful as compare to oral medications or dietary supplements.
- Topical patches cost economical to purchase.
- Applying topical patches more regularly is indicated**.**

Disadvantage of transdermal patches

- The possibility of allergic responses, such as rashes, localised eczema, and itching where the application was made.
- Medicines with hydrophilic attributes are less suited since their permeabilities are lower than those of drugs with lipophilic features.
- Drugs with molecular weights more than 1000 are difficult to absorb.

TYPES OF TRANSDERMAL PATCHES[15]

System of reservoirs

The membrane's tiny perforations, which are tucked in the middle of a backing and rate-regulating membrane, allow the medication to be released. In the drug reservoir compartment, medication is delivered as a suspension, solution and gel in a solid polymer matrix. A very thin coating of non-allergic glue is applied to the rate-regulating membrane, and this is followed by as well as a release liner and primary packing material.

System Matrixes

Drug-infused Adhesive

The original medication has been dissolved in the polymer. Then, either a hot melting procedure or solvent casting was used to apply the medicinal polymer on the backing membrane. then the reservoir is covered with glue.

Distribution of drugs

The initial medication is evenly distributed throughout the polymeric matrix. Then, an occlusive base plate-based impermeable backing layer and a medicated polymer disc are attached on top of one another. The edge of the plate is coated with adhesive rather than the pharmacological reservoir.

A Small Reservoir

It combines matrix dispersion and reservoir systems. In order to create tiny spheres of drug reservoirs, the medication is first injected into a hydrophilic polymer and then into a lipophilic polymer.

TRANSDERMAL PATCH COMPONENTS[16-17]

Backing Layer

It serves as the inner drug reservoir's thickest and most chemically resilient layer. The tensile strength and flexibility must be ideal.

Examples include polyester, polypropylene, and polyethylene (Scotchpak 1109), Ethylene vinyl acetate (CoTran 9702), polyurethane film (CoTran 9701), and an aluminium layer.

Polymeric matrix/ Drug Reservoir

Actually, rate of medication release control by uniform distribution of the medication throughout the polymeric matrix.

a) Natural polymers like chitosan and derivatives of cellulose

b) Synthetic polymers

Eudragit NE-40D, an ethyl acrylate and methyl methacrylate copolymer, Eudragit E-100, Eudragit S100, Eudragit RS PM, Eudragit RL PM and Rohm America, Piscataway, NJ, are a few examples of acrylic acid matrices.

Together, polyvinylpyrrolidone and ethyl cellulose which are hydrophobic and hydrophilic polymers, decrease the diffusion paths of pharmaceutical compounds and produce holes.

Hydrophilic Swellable Polymer Rate- Controlling Membrane

Hydroxypropylmethylcellulose (HPMC). In reservoir-type transdermal drug delivery systems, an active component is ringed by an inert membrane and is able to pass through the membrane at a controlled, regulated rate. The case in which nonporous membrane, drug transit rate is influenced by the drug solubility in membrane as well as membrane thickness.

e.g. EVA, or ethyl vinyl acetate It permits adjustment of the vinyl acetate content of polymer while maintaining membrane permeation Rubberized silicone.

Polyurethane: Condensing polyisocyanates and polyols with intramolecular urethane bonds or carbamate ester linkages yields polyurethane (-NHCOO-). To obtain the best permeability qualities, these polymers' hydrophilichydrophobic ratios can be altered.

Because they have a low penetration, hydrophilic polar chemicals are ideal for polyurethane membranes.

Adhesive

The least amount of finger pressure is necessary to keep the patch attached to the skin.

Polycrylate and Polyisobutylene (PIB), for instance.

Release Liner

While being stored and released prior to administration, the base layer avoids medication loss. It is made of materials like polyester or paper cloth.

Miscellaneous

a) Permeation-enhancing substances like menthol, limonene, and lauric acid

b) Glycerine and dibutylphthalate, plasticizers (film-forming agent)

TDDS's Compositions[18-19]

- Drug
- Polymer matrix
- Pressure sensitive adhesive
- Permeation enhancer
- Release liner
- Other excipients

Matrix of Polymers

Polymer how quickly controls the medications is released from device. Polymer cannot be used in a transdermal system unless the following requirements are met. The given polymers are useful for the TDDS.

Natural polymers:- Derivatives of cellulose, gelatine, gums, wax, natural rubber, proteins and starch.

Synthetic polymers:- Nitrile, Acrylonitrile, Butyl rubber, Hydrin rubber, Silicone rubber, Styrenebutadiene, Polysiloxane, Polybutadiene, neoprene, etc.

Semi synthetic polymer:- Polymers include polyurea, polyethylene, polyacrylate, polypropylene, polyamide, polyvinylpyrrolidone, methacrylate and polymethyl etc.

Transdermal drug delivery benefits

- Local hypersensitivity may occur at the application site. Erythema, edema, and itching can all be causing by drugs, excipients, and adhesives used in the patch formulation.
- The drug does not have a transdermal route of administration that meets the above conditions.
- The stratum corneum is impermeable to drugs having molecular weights greater than 500 Daltons.
- A significantly high or very low partition coefficient prevents the drug from entering the circulation.
- High melting point medications have lower solubility in aqueous and lipid phases.
- Nicotine patches, which deliver adjustable doses of nicotine to help smokers quit, are the most used transdermal patches in the United State. Europe approved the first e-cigarette smoking cessation patch in 2007.
- Fentanyl and buprenorphine are two opioid drugs commonly used as patches to treat chronic pain. Fentanyl is sold under the trade name Duragisic (BuTrans).
- Estrogen patches can be utilised to treat the symptoms of postmenopausal osteoporosis and menopausal.
- Contraceptive patch is another transdermal patch that delivers hormones (sold as Ortho Evra or Evra).
- A nitroglycerin patch may be used instead of a sublingual tablet to treat angina.
- Clonidine, an antihypertensive drug, is marketed as a transdermal patch under the trade name Catapres-TTS.7. Fentanyl and buprenorphine are two opioid drugs commonly used as patches to treat chronic pain. Fentanyl is sold under the trade name Duragisic (marketed as BuTrans).
- In March 2006, Emsum's transdermal MAOI form selegiline, the first antidepressant transdermal delivery system, received regulatory approval for use in the United States.

Permeability Enhancers:[20]

Compounds called permeation enhancers encourage skin permeability. They have an important role to play in a TDDS that is used to boost flux (J), the quantity of material flowing across a unit section area at specific time (t), is a Flux.

Features that make a penetration enhancer ideal:

- They need to be nontoxic, nonallergic, nonirritating, and therapeutically inert.
- It must be suitable for use with excipients and drugs.
- In the body, it must not have any pharmacological activity.
- It must be passable in terms of appearance.
- It needs to be tasteless, colourless, and odourless.
- In order to allow therapeutic drugs to enter the body inhibiting the loss of endogenous content, they should operate unidirectionally.
- It must be both physically and chemically stable.
- Its period of action must be repeatable and predictable.
- It must possess strong solvent properties.

Synthetic Permeability Enhancer:

Drug flux can be improved by chemical compounds known as accelerants or sorption promoters that temporarily weaken the skin's barrier. Chemical permeation enhancers come in many different classes, including as sulfoxides, azone analogues, fatty acids, oxazolidinones, pyrrolidones, and surfactants.

Examples:-

Dimethyl Sulphoxide, Decylmethyl sulfoxide, Oxazolidinones, Urea, Azone, Pyrrolidones, Ethanol, Isopropylalcohol, Polyethylene glycol, Propylene glycol, Glycerine, Glyceryl monocaprylate, Sefsol, Cyclodextrins, Alkyl-n, n-disubstituted aminoacetates, Sodium oleate, Palmitoleic acid, Surfactants, Span-20, Sodium Lauryl sulphate, Benzalkonium chloride, Ceramide analogues, Dendrimer.

Natural permeability enhancers:

In the context of pharmaceuticals, natural permeation enhancers present a beneficial family of transdermal drug delivery systems. NPEs are a brand-new category in the pharmaceutical industry. In the order to measure natural permeation enhancers systems and implement final dosage form manufacture on a big scale, more research is necessary.

Examples:

Camphor, Menthol, Cineole, Limonene, Euginol, Basil oil (Tulsi oil), Papain, Piperine, Enhancing skin permeability using volatile oil's sesquiterpine component, Almond oil, Vitamin E, Chitosan, Fulvic acid, Groundnut oil, Corn (maize oil), Olive oil, Ascorbic acid, Jojoba oil, Glycyrrizin, Aloe.

MATERIALS AND METHODS

Linagliptin was obtained as a gift sample from Alembic pharmaceuticals ltd, vadodara, Gujrat. HPMC K100 and Eudragit L100 are obtained from Ottochemie Pvt. Ltd and Evonik roehm pharma polymer. PEG400 purchased from Rankem, Ethanol was purchased from Rainbow international and dichloromethane from central drug house.

TRANSDERMAL PATCH FORMULATION

In this research work, preparation of a Matrix types Linagliptin transdermal patch using a solution casting technique. For this purpose, a flat circular glass mold was produced having a surface area of 15.91 cm 2 and dimensions of 4.5 cm diameter by 1 cm height.

Transdermal Patch preparation

The solution casting technique was used to create a transdermal patch. The polymers Eudragit L-100 and HPMC K-100 were dissolved in the 1:1 mixture of dichloromethane and ethanol. Until a clear solution formed, the polymer dispersion was regularly stirred using a magnetic stirrer. Drugs were dissolved in PEG 400 and Permeation Enhancer was added in it and after that it added in the polymeric solution. The homogenous mixture was then transfer in a petri dish covered with aluminium foil and kept for dry for 24 hours at room temperature. And funnel in inverted position was set over the petri dish to prevent the evaporation Dry patches were removed after 24 hours and storage in the desiccators until future study.

Table 1: Compositions of Transdermal Patch of Linagliptin

Ingredients	H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H13	H14	H15
Linagliptin (%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
HPMCK-100 (%)	1	0.2	1.8	0.2	1.8	1	1	1	1	1	1.8	0.2	1.8	0.2	1
Eudrgitl-100 (%)	0.1	1	1	0.54	0.2	0.54	0.54	1	0.54	1	0.54	0.54	0.54	0.1	0.1
PEG-400 (%)	50	30	30	10	30	30	30	50	30	10	10	50	50	30	10
Menthol (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Ethanol:DCM (ml)	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20

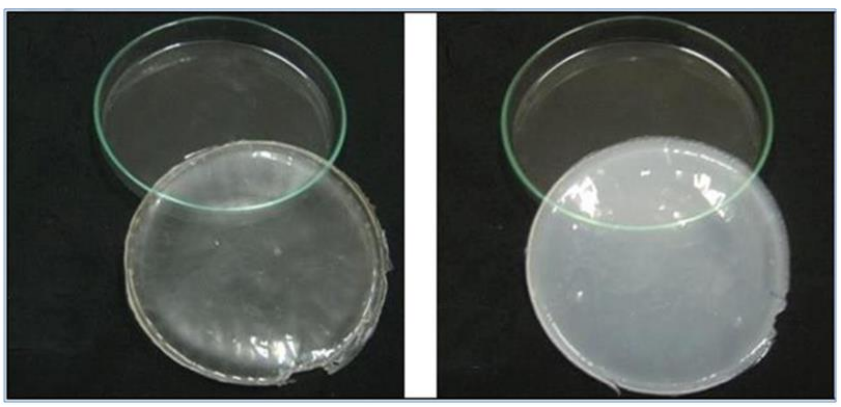

Figure 3: Image of prepared patch

Transdermal Patch's Evaluation

Physical Appearance[21]

Each transdermal patch was visually examined for flexibility, colour, and smoothness.

Thickness[22]

A screw gauge was used five times to assess thickness of a single patch. For each batch of film, the average and range of the five readings were computed.

Folding Endurance[23]

Capacity of the prepared film to be folded multiple times in the same place was carefully evaluated. A uniformly cut patch strip (2 x 2 cm2) was bent several times until it breck down. We measured the number of bends the patch could withstand at one time before it failed.

pH Determination[24]

To give the time to transdermal films for swell, they were placed in 0.5 millilitre of the double-distilled water in a glass Petri dish. The glass electrode was pushed closer to the film surface after it was given some time to align. A digital pH metre was then used to measure the surface pH, and the results were recorded.

Swelling Index[13]

The weights of the patch was determined every ten minutes following immersion in a Petri dish which contains 10 ml of phosphate buffer of 7.4 pH. The given was utilised to estimate the degree of the swelling.

$$S\,\% = \frac{(Xt - Xo}{Xo} \times 100 \quad \text{..... 2. 1}$$

Where Xt and Xo represent the weight of the patch after absorbing moisture and initial weight.

Drug Content[25]

Small sections of the transdermal film were broken out and taken in volumetric flask with a predetermined size (1 cm2). After mixing the pH 7.4 phosphate buffer, it was added and left for 24 hrs. The amount of the drug in solution was calculated using a UV spectrophotometer (Labindia). Data were collected and absorbance was measured at 241 nm.

Moisture Content Percentage

The produced films were placed at room temperature in desiccator filled with molten $Cacl_2$for 24 hours before being weighed one by one until a steady weight was achieved. The formula given below which was utilised to determine the moisture content after reweighing the film after 24 hours.

$$\%\,\boldsymbol{MoistureContent} = \frac{(\boldsymbol{Initialweight - Finalweight})}{\boldsymbol{Finalweight}} \times \mathbf{100} \quad \text{..... Equation2.2}$$

Moisture Uptake Percentage[26]

The weighted film must be stored at room temperature in a desiccator with a saturated potassium chloride solution for 24 hours to maintain 84% relative Humidity. After 24 hours, the film should be weighed once more to see how much moisture has been absorbed.

$$\%\,\boldsymbol{Moisture\ Content} = \frac{(\boldsymbol{Final\ weight - Initial\ weight})}{\boldsymbol{Initial\ weight}} \times \mathbf{100} \quad \text{... Equation 2. 3}$$

In vitro drug release[27]

Franz diffusion cells (FD) with dialysis membranes (HIMEDIA LA 395-10 MT, mean planar width - 32.34 mm, mean diameter - 21.5 mm) were used for in vitro dissolution testing. Phosphate buffer which pH 7.4 was produced through the mixture of 0.2 M sodium hydroxide (NAOH) and 0.2 M potassium dihydrogen phosphate. Sodium lauryl sulphate (0.5% w/v) was added to phosphate buffer to make pH 7.4. Phosphate buffer was placed into the diffusion cell's compartment of receptor. The dialysis membrane was washed with buffer prior to testing. The membrane was gently placed in the middle of the donor and receiver chambers of the diffusion cell. The diffusion cell was set on a magnetic stirrer and rotated constantly at a speed of 50 rpm during this period the temperature was maintained at 37 °C. Samples were collected at different intervals, and the quantity of their active component was examined. An identical phosphate buffer's volume was delivered to the receptor compartment at each sample interval in order to maintain sink conditions. The cumulative percent drug release was calculated by the measuring of the sample's absorbance at 241 nm with a UV-visible spectrophotometer.

RESULTS AND DISCUSSION

Pre formulation studies

Drug identification

The physical organoleptic characters of the powder were per standard.

Colour : Slightly yellowish

Odour : Odourless

Taste : Tasteless

State : Crystalline powder

Melting Point (MP)

Theoretical Basis melting point (MP) of linagliptin was in the ranging 190-196°C and the practical melting point of linagliptin was found 193.66 degrees Celsius.

Linagliptin's genuine actual melting point was not visible sharply because of impure samples.

Solubility Study: (Linagliptin Solubility in Surfactant)

Solubility data show that linagliptin is well soluble in liquids containing large amounts of surfactants, which may be useful in the manufacture of drug-loaded transdermal patches to enhance solubility. Linagliptin was found to be the most soluble in PEG 400. The best solubility of linagliptin in polyethylene glycol (PEG400) is utilised in the

manufacturing of transdermal patch to improve drug loading.

IR Spectra of Linagliptin

Drugs were scanned with an infrared spectrophotometer to identify them. The peak values shown on the graph were compared with those of Linagliptin. Both the study drug and linagliptin had the same peak, confirming that the study drug was linagliptin.

Calibration curve of Pure Drug:

The drug working standards were examined with a UV-Visible Spectroscopy. The absorbance of standard dilutions and calibration curve is displayed and the data shown in Table were plotted and the slope and intercept of the best-fit line were calculated. The equation of a straight line is shown in the Figure. The R2 of the straight line is found to be 0.999, meaning the values are well correlated.

Table 2: Linagliptin absorbance value at 241nm

S.No.	Conc.(µg/ml)	Absorbance
1.	10.0	.309
2.	20.0	.620
3.	30.0	.906
4.	40.0	1.222
5.	50.0	1.525

Drug Excipient Interaction Studies

In the range 4500-750 cm^{-1}, the IR absorption spectra of the active ingredients were investigated along with the excipients. The observed and reported peaks are identical and there is no significant shift or reduction in functional peaks between the Linagliptin and excipients spectra as shown by the FTIR spectra provided. This is because most of the Linagliptin peak is excipients bound. The FTIR spectra of Linagliptin, HPMC K-100, and EUDRGIT L-100.

The Linagliptin Patch was optimised utilising the response surface methodology. For optimisation, the Box-Behnken Design with three elements and three layers was utilised. The concentrations of polyethylene glycol, eudragit L-100, and HPMC K-100 were chosen as the optimisation parameters. Each of the three variables had three levels. For this set of variables, the experiment's design called for 15 runs.

Folding Endurance

Any patch's capacity to tolerate pressure applied in the form of folding at the same location without showing any signs of fracture is referred to as folding endurance. The number of the times the patch may be folded in the same spot is known as folding endurance. This is a crucial criterion for patches since the skin at the application site frequently stretches and contracts as a result of movements, and the patch needs to have the best folding endurance at that time.

Equation 3.1 and Table 3.7, which represent the ANOVA table and the folding endurance equation, respectively.

Folding endurance=9.2375 +97.5 *A+0.833333 *B+1.63125 *C……equation3.1

A noise-induced F-value this significant has a 6.43% chance of happening according to the model's F-value of 3.25. The lack of fit is not significant in comparison to the pure error, according to the F-value for the lack of fit, which is 0.48. In 81.84% of cases, noise is most likely the reason for a significant Lack of Fit F-value. A little imbalance is positive.

The P-value is when lower than 0.0500, term model is considered significant. If the value is higher than 0.1000, model terms are not significant. With a P-value 0.0153, Factor A, or the concentration of HPMC K-100, indicated a significant impact on folding endurance. The presence of a positive sign in equation 3.1's coefficient of Factor A denotes a favourable impact of HPMC concentration on folding endurance. As a result, increased folding endurance is correlated with an increase in polymer concentration.

Drug release in in-vitro

For the study of in-vitro drug release a Franz diffusion cell was used. The model fit summary of in-vitro drug release, suggested the linear model.

In-vitro drug release equation was displayed in equation 3.2. The drug release in in-vitro ANOVA table was shown. The p-value for factor 3 was 0.0054, which is less than 0.05.As a result, factor 3 (PEG400) in this model was a significant effect on drug's release in in-vitro. The equation showed that PEG-400 concentration followed by a negative sign had a diametrically opposed effect on the release of the medication in vitro. The PEG400 caused a greater release of the medication. By the coded equation can be utilised to compare the respective importance of the components by assessing the factor coefficients. As a result, factor 3 had a greater impact on in-vitro release than other factors.

In-vitro drug release = 49.0267 -1.87125 * A -1.13 * B + 4.87875 * C…equation 3. 2.

INVESTIGATION OF TRANSDERMAL PATCHES

Physical Parameters:

The generated patches with different polymer concentrations were uniformly smooth, bendable, opaque, and homogeneous. The films' thicknesses varied from 0.520 to 0.625 mm. Linagliptin patches had a swelling index that ranged from 43.45 to 62.38%.

Table 3: In-vitro release of drug from Linagliptin patches

Time	H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H13	H14	H15
.25	7.25	8.500	6	4.83	4.43	5.77	7.62	5.53	3.98	10.57	5.8	7.18	6.78	7.05	4.99
.5	8.535	10.78	6.60	6.056	5.3	6.88	7.82	7.42	5.04	11.92	8.37	9.78	9.38	7.85	6.47
0.75	10.28	11.48	7.96	7.62	6.43	8.61	8.11	9.22	7.61	12.52	10.46	12.19	12.32	10.88	8.48
1	11.27	13.62	9.95	8.84	8.38	9.60	8.82	11.06	9.85	14.27	12.88	13.65	14.36	13.52	10.05
1.5	15.06	17.10	14.25	14.15	10.44	12.07	10.64	15.36	14.75	15.58	18.59	20	19.58	19.01	14.46
2	19.78	22.35	19.24	19.78	15.54	15.32	15.87	19.99	21.2	18.38	24.38	25.34	26.6	25.66	20.52
2.5	21.46	23.45	20.93	21.72	18.95	16.97	17.18	24.37	24.39	19.05	26.58	28.73	28.59	28.54	23.19
3	24.67	24.78	23.98	27.05	21.20	19.28	19.45	26.40	27.45	19.88	29.96	31.33	32.35	31.12	26
3.5	25.89	25.68	26.98	28.99	25.99	20.58	20.12	30.89	31.15	21.75	32.83	35.47	35.95	33.28	28.94
4	28.38	30.39	29.25	31.15	28.68	23.28	22.78	34.52	34.39	23.90	36.56	37.59	37.67	36.69	30.98
5	32.20	34.04	33.01	34.55	33.38	26.32	25.07	40.35	36.85	27.39	40.44	40.99	42.68	40.60	33.78
6	35.99	38.37	35.25	37.99	36.38	28.1	27.45	44.30	37.85	28.98	43.57	44.45	45.55	43.78	37.44
7	38.99	40.78	39.85	41.54	39.38	31.78	30.17	49.56	39.80	30.45	46.25	45.95	49.84	48.20	41.96
8	45.95	46.8	45.23	47.48	49.42	35.23	31.55	55.35	41.85	32.86	52.84	48.97	52.34	50.99	48.45
24	54.51	53.99	55.62	53.92	64.78	49.95	42.15	51.05	47.52	58.66	58.51	55.53	56.55	54.11	50.68

Table 4: Physical parameters of Linagliptin patches

Formulation	Physical appearance	Thickness (mm)	% Swelling Index
H1	Smooth	0.56±0.85	45.02±0.75
H2	Smooth	0.544±0.88	43.45±0.83
H3	Smooth	0.52±0.73	50.61±0.61
H4	Smooth	0.566±0.66	57.44±0.44
H5	Smooth	0.568±0.78	53.73±0.65
H6	Smooth	0.574±0.85	45.43±0.79
H7	Smooth	0.58±0.77	55.21±068
H8	Smooth	0.603±0.56	45.18±0.75
H9	Smooth	0.588±0.58	55.73±0.86
H10	Smooth	0.594±0.86	54.35±0.68
H11	Smooth	0.604±0.79	59.77±0.58
H12	Smooth	0.625±0.85	62.38±0.69
H13	Smooth	0.6±0.89	56.24±0.57
H14	Smooth	0.59±0.84	53.18±0.68
H15	Smooth	0.626±0.78	57.25±0.88

Drug Content

Drug content guarantees that the medication is distributed consistently throughout the formulation. The formulations medication content ranges from 89.81 to 98.75%. As a result, the medication was evenly distributed throughout the patches.

Moisture Content

The content of moisture of patches' ranges from 5.2 to 8.8. Because HPMC is hydrophilic by nature, it was discovered that cases of high HPMC concentrations had greater % moisture contents.

Moisture Uptake

The patches' 5 moisture content ranged from 6.1 to 11.5. The patches that contained a lot of HPMC have shown a lot of moisture absorption.

Drug release study of optimised patches in in-vitro

A vital method for prediction how medications will behave in vivo is the in vitro release profile. To the prediction the repeatability of the duration and of rate therapeutic activity, release studies are necessary. This study makes predictions about how drugs will release from the system. Table 5 displayed the proportion of medication release. The existence of polymeric chain cross-linking networks may be the cause of this diversity in the characteristics of each patch formulation's medication release. The deliveries and intensity of the dispersion are impacted by the different diffusion pathways that transdermal patches produced from different polymeric mixtures have.

Table 5: Drug release profile in In-vitro of optimized Linagliptin patch

Time (hours)	Absorbance	Conc.(µg/ml)	Quantity Dissolved	Cum. Amount Dissolved	Cum% Drug Release
0	0	0	0	0	0
0.5	0.19	4.110898	0.008	1.23	7.82
1	0.28	6.214148	0.013	1.86	11.8
1.5	0.39	7.93497	0.016	2.38	15.12
2	0.52	10.45887	0.022	3.14	19.91
3	0.67	13.47993	0.027	4.04	25.62
4	0.82	16.19504	0.032	4.86	30.82
5	0.88	17.32315	0.035	5.2	32.93
6	0.93	18.27916	0.037	5.48	34.75
7	1.03	20.13381	0.04	6.04	38.26
8	1.06	20.68836	0.041	6.21	39.31
24	1.50	29.12048	0.058	8.74	55.34

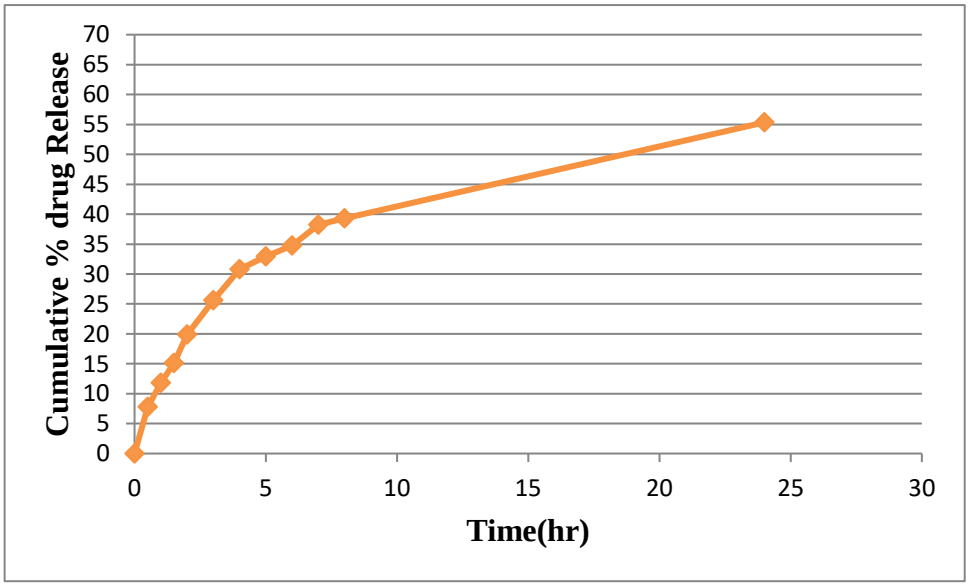

Figure 4: Drug release In-vitro from optimized Linagliptin patch

SUMMARY AND CONCLUSION

Linagliptin transdermal treatment was developed using polymers such as Eudragit L100, HPMC K 100 and menthol as permeation Enhancer in an effort to increase bioavailability. IR spectral compatibility studies designate that there were no any potential interactions in between the drug and polymer. Employing Box-responsive Behnken's surface design, the formulation was improved. Utilising a Box-Behnken structure with three tiers and three central points. According to the experimental design provided by the programme Design of Experiment, a total of fifteen formulations were developed. Software suggested the ideal patch level based on two reactions, in-vitro drug release and folding endurance. The programme proposed levels of 1.8, 0.1, 50 and 0.5 for HPMC K100, ERL100, PEG400 and Menthol, respectively. Patch thickness, medicine concentration, moisture content, moisture absorption, and swelling index were other factors considered while evaluating patches. It is found that patches created with HPMC K 100 have higher moisture content and moisture absorption rates than patches made with ERL 100 and HPMC K 100. The patches' moisture content ranges from 5.2% to 8.8%. The patches had a moisture uptake that varied from 6. to 11.5, inclusive. Additionally, the drug concentration was within allowable ranges. The formulations range in drug concentration from 90.71% to 98.75 percent. As a result, the patches were evenly sprayed with the drug. The films' thickness ranged from 0.520 to 0.625 mm. For Linagliptin patches, the swelling index ranged from 43.45 to 62.38 percent. In line with expectations, from the fifteen formulations the most improved patch which was H5 that release 64.78 percent of the drug throughout the course of 24 hours. Drug release in-vitro were all employed to evaluate the enhanced patch. The programme for this patch expected over 53% of drug release. The current investigation revealed that Linagliptin matrix transdermal patches performed better in vitro than pure medication using permeation enhancer.

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