International Journal of Medicine and Pharmaceutical Research

Journal Home Page: www.pharmaresearchlibrary.com/ijmpr

R E S E A R C H A R T I C L E

Formulation and Evaluation of Monolithic Matrix Transdermal therapeutic System of Vildagliptin using polymers Eudragit RSPO and RLPO

Kalpana Patle*, Mithun Bhowmick, Jagdish Rathi

NRI Institute of Pharmaceutical Sciences, Bhopal, India

A B S T R A C T

Diabetes Mellitus is a chronic metabolic disorder characterized by chronic hyperglycemia caused by insulin deficiency, often combined with insulin resistance resulting in the disturbance of carbohydrate, protein and fat metabolism. Anti diabetic drugs which are important for the treatment of hyperglycemic disorders are rapid and almost completely absorbed from the GIT following oral administration, but undergoes extensive first pass metabolism. The oral therapy of anti diabetic drugs also comprises problems of bioavailability fluctuations, severe hypoglycaemia and gastric disturbances. Thus, to develop safe, effective and convenient therapy has became a necessity. Hence, it is required to design a drug delivery system which may deliver anti- diabetic drugs in controlled manner for a prolonged period of time to circumvent the drug related side effects. Hence, it is required to design a drug delivery system which may deliver the drug in controlled manner for a prolonged period of time to circumvent the drug related side effects. Considering all these problems associated with oral administration of anti diabetic drug, attempt has been made to develop transdermal drug delivery system in order to achieve a better release pattern. Thus, Monolithic Matrix-type transdermal systems of Vildagliptin was formulated using polymers Eudragit RSPO and Eudragit RLPO, HPMC and Ethyl Cellulose and characterized for Thickness, Weight variation, Folding endurance, Moisture absorption, Moisture loss, Drug content, Drug–polymer interactions and In- vitro drug release studies.

Keywords: Diabetes Mellitus, Monolithic, Matrix, transdermal, Vildagliptin

A R T I C L E I N F O

***Corresponding Author**
Kalpana Patle
NRI Institute of Pharmaceutical Sciences, Bhopal, India
MS-ID: IJMPR3578

PAPER QR-CODE

A R T I C L E H I S T O R Y: Received 24 February 2018, **Accepted** 29 March 2018, **Available Online** 10 April 2018

Citation: Kalpana Patle, *et al.* Formulation and Evaluation of Monolithic Matrix Transdermal therapeutic System of Vildagliptin using Polymers Eudragit RSPO and RLPO. *Int. J. Med. Pharm. Res., 2018, 6(2): 50-61.*

C O N T E N T S

1. Introduction

Delivering medicine to the systemic circulation via skin is seen to be a desirable alternative for administrating it by mouth. The penetration across skin layer is a slow process due to the effect of the barrier properties. It offers many important advantages over oral drug delivery, e.g., avoids gastrointestinal tract and hepatic first-pass metabolism, reduces variations in delivery rates, avoids interference due

to the presence of food, controls absorption rate, increases patient compliance, suitable for unconscious patients, and enables fast termination of drug delivery, if needed. Transdermal systems are ideally suited for diseases that demand chronic treatment. Hence, anti-diabetic agents of both therapeutic and prophylactic usage have been subjected to transdermal investigation. Diabetes mellitus is a major and growing health problem worldwide and an important cause of prolonged ill health and early death. Diabetes mellitus type 2 (Noninsulin dependent diabetes Mellitus or adult-onset diabetes) is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency.[1-4] Vildagliptin is an oral anti-diabetic drug of the dipeptidyl peptidase-4 (DPP-4) inhibitor class of drug. Vildagliptin inhibits the in activation of GLP-1 and GIP by DPP-4, allowing GLP-1 and GIP to potentiate the secretion of insulin in the beta cells and suppress glucagon release by the alpha cells of the islets of Langerhans in the pancreas. After oral administration, it is rapidly absorbed from the gastrointestinal tract (GIT). The biological half-life of Vildagliptin is 1.5 hours, In order to maintain the desired blood levels for an extended period of time and reduce the frequency of administration; we have formulated the matrix-type transdermal systems of Vildagliptin using polymers Eudragit RSPO and Eudragit RLPO, HPMC and Ethyl Cellulose.

2. Materials and Methods

Materials: Drug Vildagliptin was obtained as a gift sample from spectrum lab Hyderabad. Eudragit RSPO and Eudragit RLPO, HPMC and Ethyl Cellulose from SD Fine Chem. Ltd., Mumbai. All other chemicals used were of pharmaceutical grade.

Methods

Preformulation Studies[5-10]: Preformulation study is the first step in the rational development of dosage form of a drug substance. It can be defined as an investigation of physical and chemical properties a drug substance alone and when combined with excipients.

Characterization of drug:

Physiochemical Properties of Vildagliptin

A) Physical evaluation

It refers to the evaluation by sensory characters-taste, appearance, odor, feel of the drug,

B) Solubility: Solubility of the drug was determined by taking some quantity of drug (about 1-2 mg) in the test tube separately and added the 5 ml of the solvent (water, ethanol, methanol, 0.1N HCL, 0.1N NaOH, SGF, Chloroform and acetone). Shake vigorously and kept for some time. Note the solubility of the drug in various solvents (at room temperature).

C) Melting point:

It is one of the parameters to judge the purity of drugs. In case of pure chemicals, melting points are very sharp and constant. Since the drugs contain the mixed chemicals, they are described with certain range of melting point.

Procedure for determine melting point:

A small quantity of powder was placed into a fusion tube. That tube was placed in the melting point determining apparatus (Chemline) containing castor oil. The temperature of the castor oil was gradual increased automatically and read the temperature at which powder started to melt and the temperature when all the powder gets melted.

D) Partition coefficient: It is a measurement of a drug's lipophilicity and an indication of its ability to cross cell membrane is the oil/water partition coefficient in system such as octanol/water and chloroform/water. The partition coefficient is defined as the ratio of un-ionized drug distributed between the organic and aqueous phases at equilibrium. It does provide a mean of characterizing the lipophilic/hydrophilic nature of the drug.

Procedure:

Taken well cleaned and dried separating funnel, then transferred the octanol/water system (50:50 20 ml) as sufficient quantity in separating funnel and added the 1 gm drug in it. Shaked the funnel continuously until the drug was distributed in both phases. Then placed the funnel on stand for settle both phases. After that taken both phases in beaker separately and calculated the drug amount present in both phases.

E) Determination of pH (1B w/v solution in water):

Procedure:

About 100mg of the Powder was taken and dissolved in 10ml of distilled water with sonication and filtered. The pH of the filtrate was checked with standard glass electrode.

F) Identification Test

FTIR Spectroscopy

Infra- red spectrum is an important record which gives sufficient information about the structure of a compound. This technique provides a spectrum containing a large number of absorption band from which a wealth of information can be derived about the structure of an organic compound. The region from 0.8 µ to 2.5 µ is called Near Infra-red and that from 15 µ to 200 µ is called Far infra-red region. Identification of Vildagliptin was done by FTIR Spectroscopy with respect to marker compound. Vildagliptin was obtained as White or almost white crystalline powder. It was identified from the result of IR spectrum as per specification.

Sample of pure Vildagliptin

The IR spectrum of sample drug shows the peak values which are characteristics of the drug and the graph were shown in figure 6.1

G) Loss on drying:

The moisture in a solid can be expressed on a wet weight or dry wet basis. On a wet weight basis, the water content of a material is calculated as a percentage of the weight of the weight solid. The term loss on drying, is an expression of moisture content on a wet weight basis.

Procedure:

Loss on drying is directly measured by IR moisture balance. Firstly calibrated the instrument by knob then taken 5.000 gm sample (powder) and set the temp at 100°C to 105°C for 5 minutes and constant reading set the knob and check % moisture.

H) Bulk properties

Bulk density is defined as the mass of powder divided by the bulk volume. Bulk density largely depends on particle

shape, as the particles become more spherical in shape, bulk density is increase. In addition as granules size increase, bulk density decrease. Bulk properties such as particle size, bulk density etc. of a solid form, are likely to change during process development. Therefore, comprehensive characterization of all Preformulation lots is necessary to avoid misleading predictions. Bulk Density, Hygroscopicity and Compressibility, these properties are important in designing reliable manufacturing method. Bulk density is determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder or through a volumetric measuring apparatus into a cup.

Procedure:

Accurately weighed 10gm of powder was poured into the measuring cylinder carefully level the powder without compacting, if necessary and read the unsettled apparent volume, Vo, to the nearest graduated unit. Calculate the bulk density in gm per ml, gm/cc by the formula

Bulk density = Bulk Mass/ Bulk Volume

I) Tapped density:

Tapped density is determined by measuring the volume of a known mass of powder sample before and after the tapping that has been passed through a screen into a graduated cylinder or through a volumetric measuring apparatus into a cup.

Procedure:

Accurately weighed 10gm of powder was poured into the measuring cylinder carefully level the powder and read the tapped volume (after 50-60 times tapping), V_t to the nearest graduated unit. Calculate the tapped density in gm per ml, gm/ cm^3 by the formula

Tapped density = Bulk Mass/ Tapped Volume

J) Compressibility index (Carr's index):

Compressibility index (C.I.) is an important measure that can be obtained from the bulk and tapped densities. Carr's index a material having values of less than 20% to 30% is defined as the free flowing material. It can be calculated as per given formula:

$$C.I. = \frac{100\ (V0-Vf)}{V0}$$

K) Hausner ratio: It indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density.

Hausner ratio = Tapped density / Bulk Density

L) Flow properties

Flow properties determination of powder or granules is the unique tools to avoid the weight variation of tablet Angle of repose, Carrs index, Hausner ratio are some technique by which we can estimate the flow properties of powder. The angle of repose is a relatively simple technique for estimating the flow ability of a powder through a funnel and fall freely onto a surface. The height and diameter of the resulting cone is measured and using the following equation, the angle of repose can be calculated.

$$\mathbf{Tan\ \theta = h/r}$$

Where h, r is the relatively height and radius of the powder cone. For most pharmaceutical powders, the angle of repose values range from 25 to 45, with lower values indicating better flow characteristics. Values of angle of repose ≤ 30 usually indicate a free flowing material and angle ≥40 suggest a poorly flowing material.

Procedure: Weighed 10 gm of Vildagliptin powder accurately, and passed through the funnel height up to10 cm from surface and measured the height and diameter of pile of drug sample by scale. Where h, r is the relatively height and radius of the powder pile.

M) Moisture content determination:

Principle: The titrimetric determination of water is based upon the quantitative reaction of water with an anhydrous solution of sulphur dioxide and iodine in the presence of a buffer that reacts with hydrogen ions. In the original titrimetric solution, known as Karl Fisher Reagents, the sulfur dioxide and iodine was dissolved in pyridine and methanol. The test specimen may be titrated with the reagent directly, or the analysis may be carried out by a residual titration procedure. The stoichiometry of the reaction is not exact, and the reproducibility of a determination depends upon such factors as the relative concentration of the reagent ingredients, the nature of the inert solvent used to dissolve the test specimen, and the technique used in the particular determination. Therefore, an empirically standardized technique is used in order to achieve the desired accuracy. Precision in the method is governed largely by the extent to which atmospheric moisture is excluded from the system. The titration of water is usually carried out with the use of anhydrous methanol as the solvent for the test specimen; however other suitable solvents may be used for special or unusual test specimens. (Note: Now-a-days pyridine free KF reagents are coming in which pyridine is replaced by the imidazole, because pyridine has carcinogenic effects).

Procedure

Karl Fischer volumetry is used for samples with high water content, *i.e.* 1-100 mg per sample. An iodine-containing solution serves as titrating agent. The water content of the sample is calculated using titration volume and titer of the titrating agent. One-component reagentsconveniently contain all reactants (iodine, sulfur dioxide and a base) dissolved in a suitable alcohol in one solution, whereas two-component reagents contain all necessary reactants separated in two different solutions to enhance the rapidity of the Karl Fischer reaction and the titer stability of the titrating agent. Karl Fischer coulometry is a micro-method and is particularly suitable for samples with low water content, from 10 µg up to 10 mg. Here, the required iodine is generated electrochemically in the titration vessel by anodic oxidation from iodide contained in the coulometric reagents. The amount of consumed electric charge is used to calculate the consumption of iodine and therefore the amount of water in the sample.

N) Determination of λ_{max} & Construction of Calibration curve of Vildagliptin: The λ_{max} of Vildagliptin was determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer.

Procedure:

Accurately weighed 10 mg of drug was dissolved in 10 ml of 7.2 pH buffer solution in 10 ml of volumetric flask. The resulted solution 1000µg/ml and from this solution 1 ml pipette out and transfer into 10 ml volumetric flask and

volume make up with 7.2 pH buffer solution prepare suitable dilution to make it to a concentration range of 5-25 µg/ml. The spectrum of this solution was run in 200-400 nm range in U.V. spectrophotometer (Labindia-3000).

Compatibility Studies of Drug and Excipients

In the compatibility testing program, blends of drug and excipients are prepared by triturating the drug with Individual excipients.

Procedure:

Taken 50 mg accurately weigh of Vildagliptin dry powder and 50 mg of excipients and mix the blend of drug and excipients and binary/tertiary blends of extract and excipients were prepared and transferred to inert glass vials. The mouths of the vials were covered with rubber closures followed by the aluminum seal caps. Binary/tertiary blends of extract and excipients, Vildagliptin neat and excipients were stored at 4˚C (refrigerator) as control and at 40˚C/75%RH for accelerated stability studies for 4 weeks. The visual observations (color, flow, & sticking) were recorded for initial and at the end of the first, second, third and fourth week. Therefore formulation remains stable for sufficient time.

From the FTIR data of the physical mixture it is clear that functionalities of drug have remained unchanged including intensities of the peak. This suggests that during the process drug and excipient has not reacted with the drug to give rise to reactant products. So there is no interaction between them which is in favor to proceed for formulation of transdermal drug delivery system. The FTIR study shows that the drug and excipient are compatible with each other.

Formulation Development

Preparation of Monolithic Matrix Type Transdermal Patches [12-18]

The Drug loaded monolithic matrix type transdermal patches were prepared by film casting technique. The polymers, HPMC, Ethyl Cellulose, Eudragit RLPO and Eudragit RLSO were taken in required quantity (total weight: 500 mg) as shown in the table. About 10 ml of solvent mixture of Chloroform: methanol (4:1) was added and shaked to prevent the formation of lumps, and then kept aside for swelling of polymers. And after complete solublization of polymers in mixture of solvent, added required quantity of Permeation enhancer DMSO and Plastiizer PEG 400 were added to this mixture, and vertexed. Finally weighed quantity of drug Vildagliptin (10 mg) was added to the polymer solution and mixed well. It was set-aside for some time to exclude any entrapped air and was then transferred into a previously cleaned Petri dish and then this was kept aside for solvent evaporation. The rate of solvent evaporation was controlled by inverting a glass funnel over the petri plate. After overnight, the dried films were taken out and stored in a dessicator.

Evaluation Parameters [18-23]

The prepared transdermal Patch was evaluated for the following parameters:

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 deviation.

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 endurance. The folding endurance was measured in triplicate, according to procedure and the folding endurance was found to be in the more then 250. All the patches showed satisfactory folding endurance properties. Folding endurance values of all formulation more than 250 indicating good elasticity and strength.

Percentage of Moisture Content

The prepared patches were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. 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. The formulation F1 show lowest moisture content 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 moisture uptake of F1 formulation was also low which could protect the formulation from microbial contamination reduce bulkiness.

Drug Content Analysis

The patches (n = 3) of specified area (6.16cm^2) 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 308.0 nm. The drug content analysis of different formulations was done according to the procedure given. The drug content ranged between 72±0.816% and 92±0.816%.

Scanning Electron Morphology (SEM)

The morphology of transdermal patch was performed by SEM .Firstly the sample was placed on stubs which were coated finely with gold palladium alloy and examined under microscope (JSM 6100 JEOL, Tokyo, Japan). SEM study help to investigate the surface morphology of patch. The picture of patch (F1 formulation) was clear and also show the drug was uniformly distributed in it was an optimized formulation.

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 cm^2. 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 compartment. 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.

Release Kinetics Studies

Zero order kinetics:

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation.

$$Q_t = Q_o + k_o t$$

Where, Q_t= amount of drug released in time't', Q_o= initial amount of drug in the solution, k_t= zero order release constant.

The pharmaceutical dosage forms following this profile, release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action. This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage form, as in the case of some transdermal system, as well as matrix tablets with low soluble drugs coated form, osmotic systems, etc.

First order kinetics:

The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman (1967). The following relation can express this model:

$$\text{Log } Q_t = \text{Log } Q_o + k_t t/2.303$$

Where, Q_t= amount of drug released in time't', Q_o= initial amount of drug in the solution, k_t= first order release constant. The pharmaceutical dosage forms following this dissolution profile, such as those containing water soluble drugs in porous matrices release the drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminishes.

Higuchi model:

Higuchi (1961, 1963) developed several theoretical models to study the release of water soluble drugs incorporated in semisolid and/or solid matrixes. Simplified Higuchi model can be expressed by following equation:

$$f_t = k_H t^{1/2}$$

Where, k_H= Higuchi diffusion constant, f_t= fraction of drug dissolved in time't'. Higuchi describes drug release as a diffusion process based in the Fick's law, square root time dependent. This relation can be used to describe the drug dissolution from several types modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs.

Korsmeyer-Peppas model:

Korsmeyer et al., (1983) developed a simple, semi empirical model, relating exponentially the drug release to the elapsed time (t).

$$f_t = at^n$$

Where, a = constant incorporating structural and geometric characteristics of the drug dosage form, n = release exponent, $f_t = M_t/M_\infty$ = fraction release of drug.

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, Higchi model and Korsmeyer to explain the diffusion mechanism and pattern. The % cumulative drug release was calculated over the study time range in 0-10hrs.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 F1 was to be found higher as compared to other formulation (F2, F3, F4, F5, F6).

3. Results and Discussion

Characterization of Drug:

Physiochemical Properties of Vildagliptin

A) Physical evaluation: It refers to the evaluation by sensory characters-taste, appearance, odor, feel of the drug, etc.

Table 1: List of Sensory characters

S. No.	Sensory characters	Result
1.	Taste	Tasteless
2.	Appearance	White to Off-White
3.	Odor	Odorless
4.	Texture	Crystalline

B) Solubility

Table 2: Solubility of Vildagliptin

S. No.	Solvent	Solubility
1.	Water	Freely soluble (++)
2.	Ethanol	Freely soluble (++)
3.	Methanol	Freely soluble (++)
4.	0.1N HCL	Freely soluble (++)
5.	0.1N NaOH	Poorly soluble (-)
6.	Chloroform	Poorly soluble (-)

C) Melting point:

Table 3: Melting point of the Vildagliptin

S. No	Melting Point of Vildagliptin	Average Melting Point of Vildagliptin
1.	153-155˚ C	152-153˚ C
2.	152-155˚ C	
3.	152-154˚ C	

D) Partition coefficient:

Table 4A: Partition coefficient of the Vildagliptin

S. No.	Amount of drug in octanol	Amount of drug in water
1.	370.08	440.47
2.	375.50	447.02
3.	365.25	440.06

Table 4A: Partition coefficient of the Vildagliptin

S. No.	Partition coefficient ($P_{o/w}$)	Average Partition coefficient
1.	0.84	0.84
2.	0.84	
3.	0.83	

E) Determination of pH (1 B w/v solution in water):

Table 5: pH of the Vildagliptin

S. No.	pH of the solution	Average pH of the solution
1.	7.7	7.7
2.	7.7	
3.	7.8	

F) Identification Test

Sample of pure Vildagliptin: The IR spectrum of sample drug shows the peak values which are characteristics of the drug and the graph were shown in figure 1

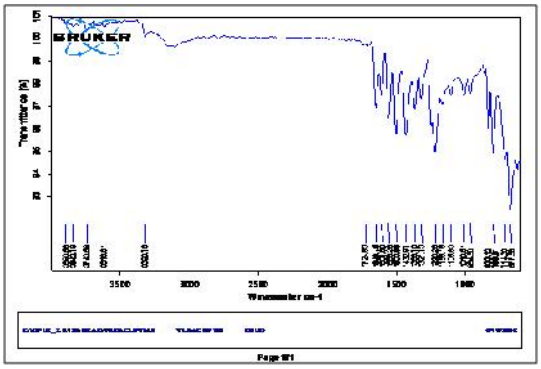

Figure 1: FT-IR Spectrum of Pure Drug (Vildagliptin)

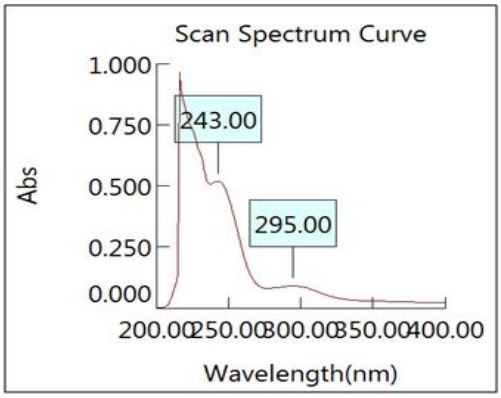

Figure 2: Standard calibration curve of Vildagliptin

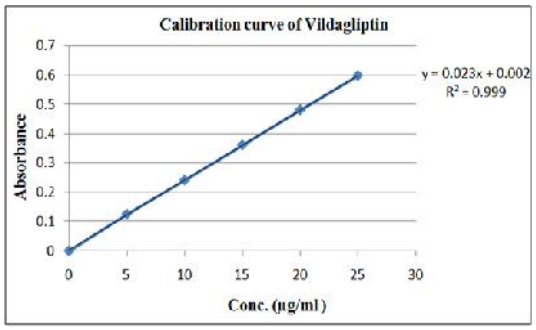

Figure 3: The linear regression analysis for standard curve

The linear regression analysis was done on Absorbance data points. The results are as follow for standard curve

Slope = 0.023

The intercept = 0.002

The correlation coefficient (r^2) = 0.999

Compatibility Studies of Drug and Excipients

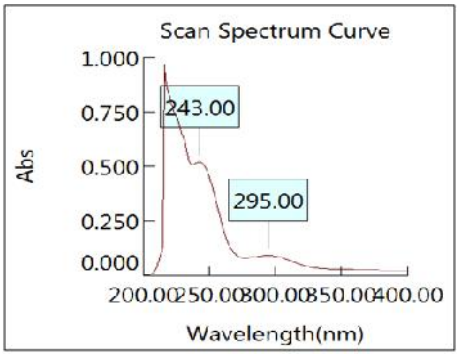

Figure 4: U.V. Graph of standard Vildagliptin

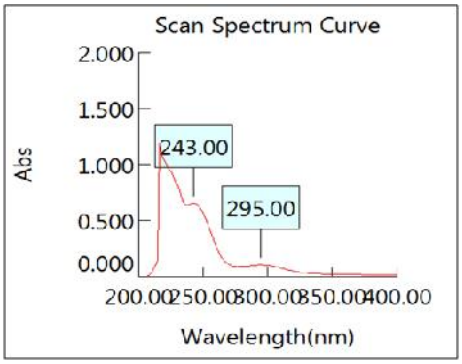

Figure 5: U.V. Graph of standard Vildagliptin + All Excipients

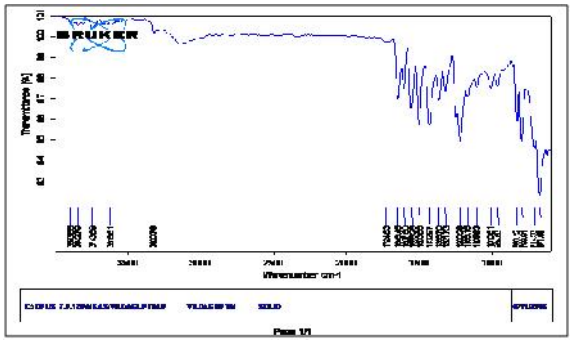

Figure 6: I.R Spectra of standard Vildagliptin

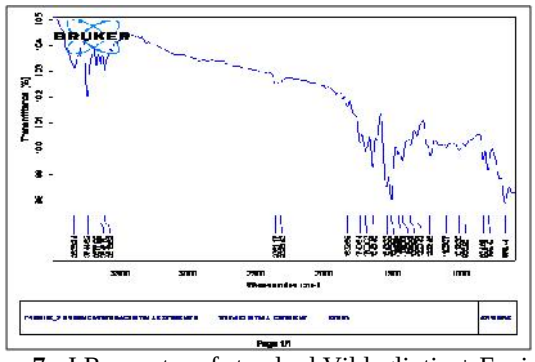

Figure 7: I.R. spectra of standard Vildagliptin + Excipient

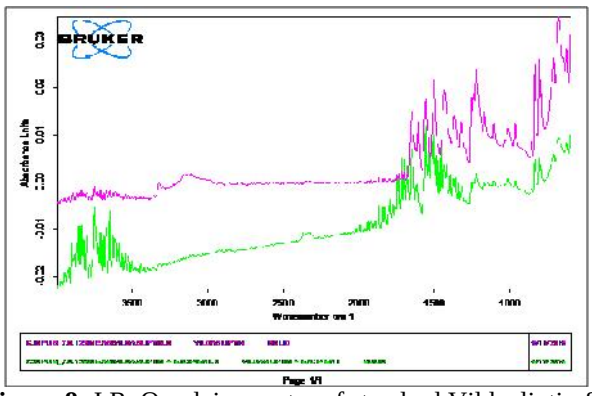

Figure 8: I.R. Overlain spectra of standard Vildagliptin & Vildagliptin+Excipient

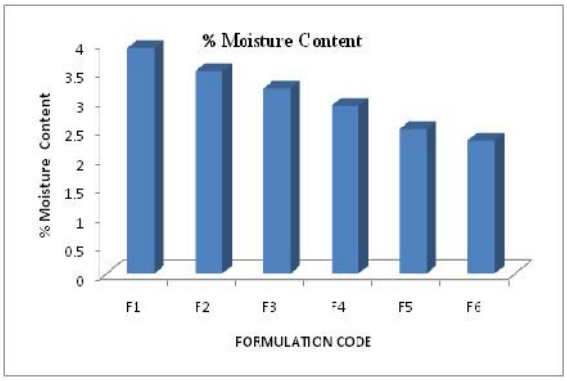

Figure 9: Moisture Content of Formulations F1 to F6

The formulation F1 show lowest moisture content 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.

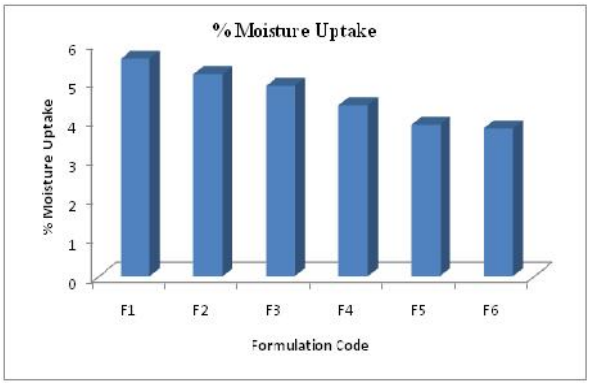

Figure 10: Moisture Uptakes of Formulations F1 to F6

The moisture uptake of F1 formulation was also low which could protect the formulation from microbial contamination reduce bulkiness.

Drug Content Analysis:

The drug content analysis of different formulations was done according to the procedure given in section 6.3.6. The drug content ranged between 72±0.816% and 92±0.816%.

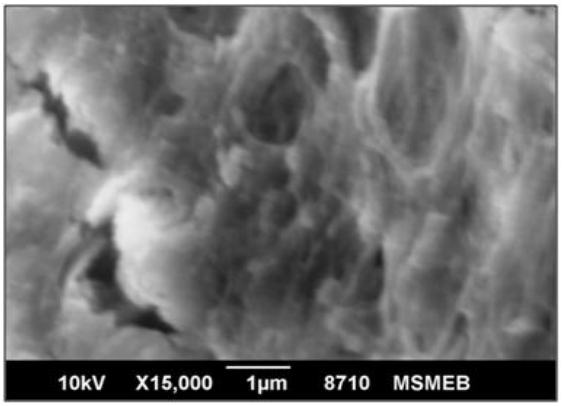

Figure 11: SEM Image of F-1 formulation

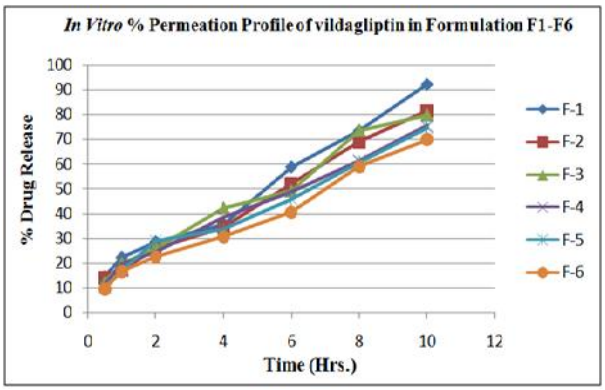

Figure 12: *In-Vitro*% Permeation Profile of vildagliptin in Formulation F1-F6

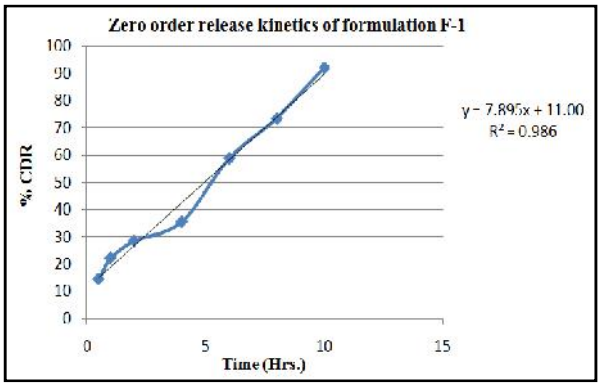

Figure 13: Zero order release kinetic profile of Formulation F1

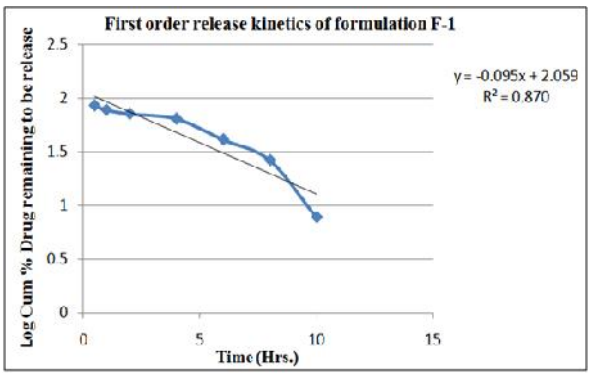

Figure 14: Zero order release kinetic profile of Formulation F1

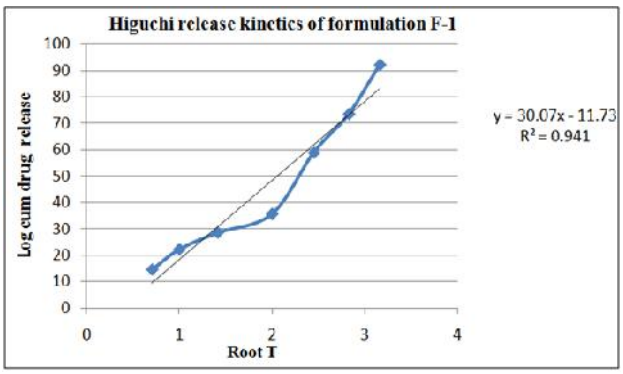

Fig 15: Higuchi release kinetic profile of Formulation F1

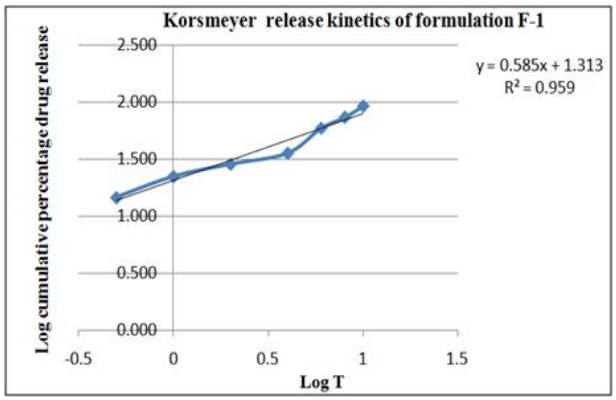

Fig 16: Higuchi release kinetic profile of Formulation F1

Discussion

Preformulation Studies

Physical properties of Vildagliptin

A. Physical evaluation: The physical evaluation was done by visual inspection. The Color was found to be White to off white powder, Odor was found to be Odorless, Taste was found to be Tasteless and texture was found to be Crystalline in nature.

B. Solubility

Solubility study of vildagliptin has has been done in various solvent such as water, ethanol, methanol, acetone 0.1 N NaOH and 0.1N NaOH solution. We were found that a solubility of Vildagliptin was good in a water, Ethanol, Methanol, 0.1 N HCl solution and poorly soluble in 0.1 n NaOH and chloroform.

C. Melting Point:

Result: Melting point was determined by Melting point apparatus at 152-153˚ C**.** The high melting point of drug was important for its sustained release floating property of tablets.

D. Partition coefficient:

Result: The partition coefficient was found to be **0.84.** It indicated that the drug was hydrophilic in nature.

E. Determination of pH (1B **w/v solution in water):**

Result: The pH determination of Vildagliptin was done by Digital pH meter and found to be **7.7**

. It means the drug was very weak acidic in nature.

F. Identification test by FTIR

Identification of Vildagliptin was done by FTIR Spectroscopy with respect to market compound. Vildagliptin was obtained as White or almost white crystalline powder. It was identified from the result of IR spectrum as per specification. The IR spectrum of sample drug shows the peak values which are characteristics of the drug and the graph were shown in figure **6.1**

G. Loss on Drying (LOD):

Result: The percentage of loss on drying was found to be **1.672 %w/w**. It means drug was free flowing in nature.

H. Flow property of Vildagliptin:

1. Bulk density: Untapped Density of the Vildagliptin was found to be 0.454 g/ml and Tapped Density (after 50 tapping) was 0.833, which results less than 1.83 Hausner ratio which denote its good flowing property

2. Compressibility Index (%)

Result: The compressibility index of Vildagliptin was found to be **45.45%.** The % compressibility of the drug was denoting its poor flow ability.

3. Hausner ration:

Result: The Hausner ration of Vildagliptin was found to be **1.83.** This value was coming in the range of 1.3-1.5, which denoted its good flowing property.

4. Angle of Repose

Result: The Angle of repose of Vildagliptin was found to be **25** degree. The value of angle of repose was ≤ 30 which indicated its free flowing property.

Result: Particle size passed through 40# was **100 (%w/w).**

I. Moisture content determination by Karl-Fischer Apparatus (KF)

Result: The Moisture content of Vildagliptin was found to be **0.113%.** It indicated that the drug sample was properly dried and have free flowing ability.

Determination of λ_{max} of Vildagliptin:

Result: The λ_{max} of Vildagliptin was determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer. The spectrum of this solution was run 200-400nm range in U.V. spectrophotometer (Labindia-3000+). The λ_{max} of Vildagliptin was found to be 243.0 nm.

Standard Calibration curve of Vildagliptin:

The standard solution of drug was prepared in different conc. in 7.2 pH buffer solution and plotted the graph between conc. and absorbance. The plot of absorbance vs. concentration was plotted and on the absorption point the linear line was determined. Which follows Beer,s Lambert law. The linear regression analysis was done on Absorbance data points. The value of Slope, Intercept and Correlation coefficient were found to be 0.023, 0.002 and 0.999 respectively.

Drug Excipient Compatibility study by U.V and FTIR

From the U.V and FT-IR data of the physical mixture it is clear that functionalities of drug have remained unchanged including intensities of the peak. This suggests that during the process drug and excipient has not reacted with the drug to give rise to reactant products. So there is no interaction between them which is in favor to proceed for formulation of transdermal drug delivery system. The FTIR study shows that the drug and excipient are compatible with each other.

Optimization of Transdermal drug delivery System

In the optimization, The Thickness, Folding Endurance, Tensile Strength, Percentage of Moisture Content, Percentage of Moisture Uptake, Drug Content Analysis,

Scanning Electron Morphology (SEM), In all six formulation Variable amount of polymer used, in all formulation F-1 was found to be most appropriate in all formulation.

In-vitro drug release studies:

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, Higchi model and Korsmeyer to explain the diffusion mechanism and pattern. The % cumulative drug release was calculated over the study time range in 0-10hrs.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 F1 was to be found higher as compared to other formulation (F2, F3, F4, F5, F6) before and after ageing/storage and all was in acceptable limits. Therefore formulation remains stable for sufficient time.

Table 6: Loss of drying of drug sample

S. No.	Initial weight	Final weight after 5 minutes	% loss of drying	Avg. % loss of drying
1.	5gm	4.92 gm	1.67 %	1.672 %
2.	5gm	4.91 gm	1.82 %	
3.	5gm	4.92 gm	1.67 %	

H) Bulk properties

Table 7: Bulk density of Vildagliptin

S. No.	Bulk mass	Bulk volume	Bulk density	Avg. bulk density
1.	10 gm	22 ml	0.454 g/ml	0.454 g/ml
2.	10 gm	22 ml	0.454 g/ml	
3.	10 gm	22 ml	0.454 g/ml	

I) Tapped density:

.

Table 8: Tapped density of Vildagliptin

S. No.	Bulk mass	Tapped volume	Tapped density	Avg. tapped density
1.	10 gm	12 ml	0.833 g/ ml	0.833 g/ ml
2.	10 gm	12 ml	0.833 g/ ml	
3.	10 gm	12 ml	0.833 g/ ml	

J) Compressibility index (Carr's index):

Table 9: C.I. of Vildagliptin

S. No.	Bulk density	Tapped density	C.I.
1.	0.454 g/ml	0.833 g/ml	45.49

K) Hausner ratio:

Table 10: Hausner of Vildagliptin

S. No.	Bulk density	Tapped density	Hausner ratio
1.	0.400 g/ ml	0.555 g/ ml	1.83

L) Flow properties

Table 11: Angle of repose of Vildagliptin

S. No.	Height of pile	Radius of pile	Angle of repose	Avg. angle of repose
1.	2.3 cm	5 cm	25 º	**25 º**
2.	2.4 cm	5.1 cm	25 º'	
3.	2.5 cm	5.4 cm	25 º	

M) Moisture content determination:

Table 12: Moisture content determination

S. No.	Drug	KF Factor	Amount of KF Reagent consumed	Moisture content
1	Vildagliptin	0.512	0.15ml	0.078

Table 13: Calibration curve of Vildagliptin

S. No.	Conc. (µg/ml)	Absorbance (λ max at 243nm)			
		I	II	III	Average
1	5	0.096	0.097	0.098	0.097
2	10	0.187	0.196	0.187	0.190

3	15	0.27	0.276	0.275	0.274
4	20	0.349	0.348	0.351	0.349
5	25	0.443	0.444	0.445	0.444

Table 14 Different Formulation used for Optimization TDDS

Formulation Code	Drug (mg)	HPMC (mg)	RLPO (mg)	RSPO (mg)	Ethyl cellulose (mg)	Total polymer weight (mg)	Plasticizer % w/w	Permeation Enhancer % w/w
F1	10	400	50	-	50	500	0.5	10
F2	10	300	100	-	100	500	0.5	10
F3	10	200	150	-	150	500	0.5	10
F4	10	400	-	50	50	500	0.5	10
F5	10	300	-	100	100	500	0.5	10
F6	10	200	-	150	150	500	0.5	10

Table 15: Thicknesses and Folding Endurance of Different Formulations

S. No.	Formulation Code	Thickness (µm)*	Folding Endurance*
1.	F1	91±1.23	MT 250±2
2.	F2	92±0.89	MT 250±3
3.	F3	92±0.95	MT 250±5
4.	F4	90±1.10	MT 250±6
5.	F5	91±0.85	MT 250±3
6.	F6	92±1.05	MT 250±3

Table 16: Moisture Content and Moisture Uptake of Different formulations

S. No.	Formulation Code	% Moisture Content	% Moisture Uptake
1.	F1	3.9	5.6
2.	F2	3.5	5.2
3.	F3	3.2	4.9
4.	F4	2.9	4.4
5.	F5	2.5	3.9
6.	F6	2.3	3.8

Table 17: Percentage Drug Content of all the Formulations

S. No	Formulation Code	% Drug Content
1	**F1**	99.00±0.81
2	**F2**	92.00±3.74
3	**F3**	91.56±4.18
4	**F4**	87.00±0.81
5	**F5**	80.58±3.20
6	**F6**	98.80±0.81

Table 18: *In Vitro*% Permeation Profile of vildagliptin in Formulation F1-F6

Time	% of Drug Release					
(hr)	F1	F2	F3	F4	F5	F6
0.5	12.19	13.9	15.6	12.00	12.9	14.2
1.0	17.41	17.09	18.2	19.6	17.00	16.5
2.0	25.8	26.05	26.05	24.6	28.90	27.6
4.0	35.6	37.8	40.00	38.3	44.01	46.5
6.0	51.8	52.03	49.05	55.23	56.01	53
8.0	62.6	68.9	69.90	65.0	71.1	75.01
10.0	86.0	84.00	80.01	83.06	82.60	79.00

Table19: Kinetic data of vildagliptin transdermal patches of Formulation F1

Formulation code	Regression coefficient			
	Zero order	First order	Higuchi	Korsmeyer
F1	0.986	0.870	0.941	0.959

4. Conclusion

It was concluded that the monolithic matrix transdermal patches of Vildagliptin were successfully developed in order to sustain the drug release rate by using Eudragit RLPO, RSPO, HPMC, EC as release retardant.

6. References

[1] Vyas SP, Roop RK. Controlled drug delivery concepts and advances. New Delhi: Vallabh prakash publishers. 2002.

[2] Brahmankar DM, Jaiswal SB. Biopharmaceutics and pharmacokinetics a treatise. Reprint of 1st Edn. Delhi: vallabh prakashan; 2003.

[3] Chien YW. Transdermal therapeutic systems. In: Robinson JR, Lee V. H. editors. Controlled drug delivery: Fundamentals and applications. 29th Ed. New York: Marcel Dekker; 1987

[4] Chien YW. Novel drug delivery systems. 2nd edn. New York: Informa healthcare ; 1992

[5] Kerimoğlu O, Keskin E, Dortunç B, Anah S.,, Acta Pol Pharm. 2013 Mar-Apr,70(2): 291-300.

[6] Satheeshababu BK, Shivakumar KL. Synthesis of conjugated chitosan and its effect on drug permeation from transdermal patches. Indian J Pharm Sci. 2013 Mar; 75(2):162-70.

[7] Baviskar DT, Parik VB, Jain DJ. Development of Matrix-type transdermal delivery of lornoxicam: in vitro evaluation and pharmacodynamic and pharmacokinetic studies in albino rats.PDA J Pharm Sci Technol. 2013 Jan-Feb, 67(1): 9-22

[8] Kshirsagar SJ, Bhalekar MR, Mohapatra SK, Development and evaluation of carvedilol-loaded transdermal drug delivery system: In-vitro and in-vivo characterization study. Drug Dev Ind Pharm. 2012 Dec;38(12):1530-7.

[9] Asgar Ali, Anupam Trehan, Zabih Ullah, Mohammed Aqil, Matrix type transdermal therapeutic systems of glibenclamide: Formulation, ex vivo and in vivo characterization, Yasmin Sultana, Drug Discoveries & Therapeutics. 2011; 5(1):53-59.

[10] Shyam Sunder Agrawal, Jatin Kumar Pruthi, Development and evaluation of matrix type transdermal patch of ethinylestradiol and medroxyprogesterone acetate for anti-implantation activity in female Wistar rats, Contraception, Volume 84, Issue 5, November 2011, Pages 533–538

[11] Hans G. Kress, Hildegard Boss, Thomas Delvin, Gezim Lahu, Søren Lophaven, Michael Marx,Sophie Skorjanec, Thomas Wagner, Transdermal fentanyl matrix patches Matrifen and Durogesic DTrans are bioequivalent., European Journal of Pharmaceutics and Biopharmaceutics 75 (2010) 225–231.

[12] M. Shahbaz Shams, M. Intakhab Alam, Asgar Ali, Yasmin Sultana and M. Aqil. Pharmacodynamics of a losartan transdermal system for the treatment of hypertension Losartan transdermal system Drug Development and Industrial Pharmacy, 2010; 36(4): 385–392

[13] A novel poly methyl methacrylate hydrophilic adhesive matrix intended for transdermal patch formulations Francesco Cilurzo, Paola Minghetti, Chiara G.M. Gennari , Antonella Casiraghi, and Luisa Montanari, Drug Delivery, 2010; 17(3): 171–177

[14] Eudragit-based transdermal delivery system of pentazocine: Physico-chemical, in vitro and in vivo evaluations Ashok R. Chandak and Priya Ranjan Prasad Verma, Pharmaceutical Development and Technology, 2010; 15(3): 296–304

[15] Randomised, cross-over, comparative bioavailability trial of matrix type transdermal drug delivery system (TDDS) of carvedilol and hydrochlorothiazide combination in healthy human volunteers: A pilot study ,Shyam S. Agrawal, Ashish Aggarwal, Contemporary Clinical Trials 31 (2010) 272–278

[16] Design and evaluation of monolithic drug-in-adhesive transdermal patches of meloxicam. Somasundaram jayaprakash, sundarapandian ramkanth, posina anitha, muthumanickam alagusundaram, mohamed t s saleem and madhusudhana c chetty, Malaysian Journal of Pharmaceutical Sciences Vol. 8, No. 2, 25–43 (2010)

[17] Formulation and evaluation of transdermal patches of papaverine hydrochloride Samip S Shah, Joshi Rahul, Prabhu Prabhakar, Asian Journal of Pharmaceutics - January-March 2010,79-86

[18] Priyanka Shrestha, Shiva Kumar Bhandari, SM Ashraful Islam, Md Selim Reza and Santosh Adhikari, Design and Development of Immediate and Sustained Release Tablets of Vildagliptin, Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2014,RJPBCS, 5(4), Page No. 811

[19] Y. Ganesh Kumar, J. Sreekanth, D. Satyavat, Formulation Development and Evaluation of Sustained Release Matrix Tablets of Vildagliptin - Synthetic and Natural Polymers, Asian Journal of Pharmaceutic, Oct-Dec 2015, 9 (4)

[20] M. Sunitha Reddy and Mohd Shoeb Ahmed, Formulation and evaluation of sustained release vildagliptin matrix tablets by using pectin natural polymers as release retardant, WJPPS, Vol 4, Issue 10, 2015.

[21] Mahesh Attimarad, Sree Harsha Nagaraja, Bandar E Aldhubaib, Anroop Nair and Venugopala K N, Simultaneous Determination of Metformin and Three Gliptins in Pharmaceutical Formulations Using RP HPLC: Application to Stability Studies on Linagliptin Tablet Formulation, Indian Journal of Pharmaceutical Education and Research, Vol 48, Issue 4, Oct–Dec, 2014

[22] Shaik. Allabaksh, Debjit Bhowmik, Nanda Kishore Agarwal, K.P. Sampath Kumar, Praveen

Khirwadkar, Formulation and evaluation of vildagliptin sustained release tablets, Indian Journal of Research in Pharmacy and Biotechnology, IJRPB, 2(4), 2014: 1293

[23] Y. Ganesh Kumar, J. Sreekanth and D. Satyavati, Formulation design and development of SR matrix tablets of vildagliptin by using different grades of carbopol and eudragit, Journal of Chemical and Pharmaceutical Research, 2015, 7(5):1213-1224.