IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

FORMULATION OPTIMIZATION AND EVALUATION OF TRANSDERMAL PATCH OF VILDAGLIPTIN FOR TREATMENT OF DIABETES MELLITUS

[1]Pallavi M. Chaudhari,[2]Aarti V. Paithankar

[1]Associate Professor, Department of Pharmaceutics. Dr. D.Y. Patil College of Pharmacy.[2]PG student, Dr.D.Y.Patil College of Pharmacy, Akurdi, Pune,

Abstract: Increasing research interest has been focused on controlled drug delivery using natural and biocompatible polymers as drug carriers in recent years. In the present study transdermal patch of Vildagliptin was developed using Aloe Vera gel powder as a polymer and Almond oil as penetration enhancer. Patches were prepared by solvent evaporation technique. Optimization was carried out by response surface methodology using central composite design with polymer concentration(X1), plasticizer concentration(X2), and concentration of permeation enhancer(X3) as independent variables. Hydrophilic nature of polymer as well as plasticizer and Interaction withintercellular protein to disrupt the structure of stratum corneum were responsible for increase in drug release with increase in their concentrations. Optimized formulation F9 exhibited high drug release, folding endurance Thus, It can be concluded that transdermal patch of Vildagliptin using aloe vera gel powder will be more efficacious and gives synergistic effect to drug.

***Index Terms*– Central Composite, Transdermal patch, Aloe Vera gel powder, Vildagliptin, Almond oil.**

1. Introduction

Diabetes mellitus is a muddled metabolic issue portrayed by hyperglycaemias, irregularities in lipids, carbohydrates, proteins digestion which prompts postprandial and fasting hyperglycaemias, dyslipidaemia and hyperinsulinemia. Diabetes mellitus is a major health problem growing day by day all over the world and cause of early death.

Several hypoglycaemic agents present in market which works by different mechanism, like sulfonyl urea's, biguanides, thiazolidinediones etc. Currently, incretin-based therapy has been approved by US FDA to treat type II diabetes mellitus, theywork by inhibiting Dipeptidylpeptidase-4 enzyme (DPP-4) and maintain adequate glycaemic control. Vildagliptin is competitive inhibitor of DPP4 and it allows GLP and GIP to increase the secretion of insulin in beta cells and suppress glucagon release by alpha cells in islets of Langerhans's of pancreas. To enhance GLP activity, inhibition of the DPP-4 enzyme is emerging as a novel therapeutic approach in the treatment of diabetes. It has a many advantage and beats the significant issues, for example, hypoglycaemia and weight gain, the typical symptoms of other oral hypoglycaemic agents. However, its utilization has been limited because of a few antagonistic impacts, for example hepatotoxicity and ordinary hepatic capacity tests are prescribed because of worries about liver damage. Vildagliptin possess distinctive physiochemical properties, such as poor water solubility, small molecular mass and suitable melting point. which proposes its possibilities to be conveyed through the skin. Formulating a transdermal drug delivery product of this drug is probably going to defeat the hepatic unfriendly impacts and could maintain appropriate blood level for a prolonged period of time.[1]

Transdermal drug delivery system is characterized as discrete dosage form which applied to skin, convey the drug at a controlled manner in a systemic circulation while bypassing first pass effect. This delivery system offers a worthwhile option in contrast to conventional delivery systems, for example, injections or oral delivery. This approach builds the therapeutic effectiveness of pharmaceutical actives by avoiding first pass metabolism, delivers drug molecules in controlled manner, enhances absorption, and improves patient compliance.[2]

Present investigation involves the use of natural polymer such as Aloe vera gel powder. It has various advantages such as enhance the intestinal absorption, effective delivery of poorly absorbable drugs, Sustained release of pharmaceutical dosage form, and also gives synergistic effect to anti diabetic drugs.[3]

The objective of this study was to develop Matrix type transdermal patch of Vildagliptin with natural polymer and permeation enhancer for the treatment of diabetes mellitus. The transdermal drug delivery system was optimized using central composite design. The patches were evaluated for diffusion studies, folding endurance, drug content, etc.

2. Materials and Methods

2.1 Material:
Vildagliptin was obtained as gift sample from Alkem laboratories, Taloja, Mumbai. And the Aloe vera Gel powder was gifted from Maple Biotech pvt.ltd Bhosri, Pune. All other Chemicals and excipients used were of analytical reagent grade.

2.2 Methods:

2.2.1 Preformulation studies:

Preformulation study is the initial phase in the objective development of dosage form of a drug substance. It is characterized as an examination of physical and chemical properties of drug substance alone and when combined with excipients. Such as physical appearance, melting point, Partion coefficient, uv analysis, compatibility studies of drug and excipients. [4]

2.2.2 Pre-optimization study:

Preliminary introductory batches were prepared utilizing the polymer Aloe vera gel powder in various fixations, no drug was included for this screening. Additionally, propylene Glycol and Glycerin were utilized. These batches were prepared to set the lowest and effective concentration of both polymers and plasticizer. (Figure no.1)

2.3 Experimental Design:

Response surface methodology (RSM) is one of the popular methods in the development and optimization of drug delivery systems. Based on the principles of design of experiments (DOE), the methodology involves the use of various types of experimental designs, generation of polynomial mathematical relationships and mapping of the response over the experimental domain to pick the optimum formulation. Central composite design (CCD) having 3- independent variables at 2-level is one of the RSM designs available for statistical optimization of the formulations. [5]
Optimizations of transdermal patches were performed using a randomized response surface central composite design. This design was carried out with Design Expert 12 software to review effect of three independent factors on response variables like drug release (Y_1), folding endurance (Y_2). The three factors were concentration of polymer (Aloe Vera gel powder) (X_1), concentration of plasticizer (PG)(X_2), and concentration of permeation enhancer (almond oil) (X_3).

2.2.4 Development of transdermal patch by solvent evaporation technique:

Patches were prepared by solvent evaporation method.[2] The polymer was taken in various concentrations and dissolved in 10ml of solvent mixture of water: methanol (3:2) .and stirred under magnetic stirrer with 200Rpm to form clear solution and kept aside to make free from bubbles. After complete solubilization of polymer in a mixture of solvent, added required quantity of plasticizer propylene glycol and permeation enhancer almond oil were added to this mixture and stirred. Finally weighed quantity of drug Vildagliptin was added to this polymer solution and mixed well. It was set aside for some time to get rid of any air bubbles and then transferred to 56.71cm^2 diameter glass Petri dishes and dried at 40◦C. Dried films were removed carefully from Petri dishes and stored in desiccators.

Figure 1: preliminary trial batches

Table:1 formula for vildagliptin patch as per central composite design.

Formulation code	Drug (Vildagliptin) [mg]	Concentration of Aloe vera gel powder [mg] (X_1)	Concentration of propylene glycol [%w/w] (X_2)	Concentration of Alomond oil [%w/w] (X_3)
F1	141.8	0	0	0
F2	141.8	-1	0	0
F3	141.8	1	1	-1
F4	141.8	0	0	-1
F5	141.8	0	-1	0
F6	141.8	-1	1	-1
F7	141.8	-1	1	1
F8	141.8	1	1	1
F9	141.8	0	0	1
F10	141.8	-1	-1	1
F11	141.8	1	0	0
F12	141.8	0	1	0
F13	141.8	1	-1	-1
F14	141.8	-1	-1	-1
F15	141.8	1	-1	1

3. Evaluation Parameters of Transdermal Patch:

3.1 Thickness:
The thicknesses of the formulated patches were measured at four different points using vernier calipers and average thickness was calculated.[6]

3.2 Folding Endurance:
The patch of specific area (2cm ×2cm) was cut and repeatedly folded in the same place until it broken. The number of times film could be folded at the same place without breaking gave the value of folding endurance.[7]

3.3 Drug Content:
A specified area of patch (2cm×2cm) was dissolved in 10ml of methanol in volumetric flask and diluted into 100ml with methanol and stir continuously with the help of shaker. After filtration the drug was estimated by UV spectrophotometer at 209nm and determined the drug content.

3.4 Surface pH:
The surface pH of the specified patch was determined by placing the pH meter in close contact with the wetted surface of patch. The pH of selected patch was measured using a pH meter.[8]

3.5 Percent Moisture content:
The films were weighed individually and kept in a desiccator containing activated silica at room temperatures for 24hr. [9] Individual films were weighed repeatedly until they show constant weight. Percentage moisture content was calculated by using subsequent formula:

Percent moisture content=

Initial weight- final weight/ final weight×100

3.6 Percent Moisture uptake:
The films were also subjected to moisture uptake studies by exposing the patches to 84% RH and ambient temperature in a desiccator containing saturated solution of potassium chloride until a constant weight was achieved. [10] Then the films were weighed and percentage moisture uptake was calculated by using the following formula:

Percentage moisture uptake=

Final wt – initial wt/ initial wt×100

3.7 In Vitro drug release studies:
In Vitro drug release studies were performed by using a Franz diffusion cell witha receptor compartment capacity of 20mL.The cellophane membrane was used for the determination of drug from the prepared transdermal matrix-type patches. The cellophane membrane was mounted between the donor and receptor compartment of the diffusion cell.The prepared transdermal film was placed on the cellophane membrane. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.2.The whole assembly was fixed on a hot plate magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads, and the temperature was maintained at 32±0.5◦C, because the normal skin temperature of human is 32◦C.The samples were withdrawn at different time intervals and analyzed for drugcontentspectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.[11]

3.8 Stability studies

The stability studies were conducted as per ICH guidelines to investigate the influence of temperature and relative humidity on the drug content in different formulations. Films were placed in a glass beaker lined with aluminium foil and kept in humidity chamber maintained at 40 ± 2c and 75 ± 5% RH.The optimized transdermal formulations were subjected to stability studies for 3 months as per ICH guidelines. Samples were taken after third month and evaluated for percent drug content, folding endurance.[12]

4. Result and Discussion:

4.1 Organoleptic properties of drug:

The color, odor and taste of the drug were characterized and recorded using descriptive terminology; the results are shown in Table2:

Table 2: results of organoleptic properties of Vildagliptin

Sr. No.	**Parameter**	**Observation**
1	Color	White
2	Taste	Tasteless
3	Odor	Odorless
4	Appearance	White Crystalline Powder

4.2 physiochemical studies:

Aloe vera gel powder was subjected to preliminary study to confirm the nature of obtained powder. The tests performed were determine the presence of alkaloids, amino acids, minerals, proteins, and polysaccharides.

Table 3: tests for aloe vera gel powder

Sr no.	Phytochemical tests	Observations	Results
1	Wagners test (for alkaloids)	Reddish brown ppt	Passes
2	Mayers test (for alkaloids)	Ppt observed	Passes
3	Dragandroff test (for alkaloids)	Orange ppt	Passes
4	Test for carbohydrates (molisch test)	Violet ring formed at junction	Passes
5	Tests for proteins (Biuret test)	Pink colour appears	Passes

4.3 Solubility of drug:

The solubility of the drug was checked in different solvents. This might be helpful in selection of a suitable solvent to dissolve drug as well as excipients used in formulations. Solubility of drug depends on pH, ionic strength, temperature, buffer concentration.

Table 4: Solubility Data of Vildagliptin

Sr. No.	**Solvent**	**Solubility**
1	Methanol	Freely soluble
2	Ethanol	Slightly soluble
3	Distilled water	Very slightly Soluble
4	Chloroform	Soluble
5	Buffer 7.2	Slightly soluble

4.4 Melting Point:

The melting point was found to be 153-154◦C by capillary method

4.5Partioncoeffient:

The partition coefficient of Vildagliptin was calculated from the ratio between the concentration of Vildagliptinin organic and aqueous phase using following:

$$P_{o/w} = (C_{oil} / C_{aqueous})$$

The partition coefficientof drug was found to be 1.32

4.6 Pre optimization results:

The Aloe vera gel powder used as polymer which is used in various concentrations produced sticky and opaque patches. The lowest concentration of polymer gaves thin patches. The proper concentration of plasticizer gaves plasticity and strength to the patches. The glycerin used in patches produced sticky patches which were not dried properly. And patches with propylene glycol as plasticizer had very good film properties. The polymer concentration which produced transparent and flexible patches with smooth appearance were found to be in range 300to 400mg with propylene glycol as plasticizer, almond oil as permeation enhancer using water and methanol(3:2) as a solvent system.

4.7 Drug polymer compatibility studies

Drug- Excipient interactions play a vital role in the release of drug from formulations. The pure drug Vildagliptin and its mixture with aloe Vera gel powder was mixed separately with IR grade KBr and was scanned over a range 400-4500 cm^{-1} using FTIR instrument (FTIR-IRAffinity-1S, Shimadzu, Japan.).The drugexhibits peaks due to carboxylic group, alcohol group, secondary amine, and C=O Stretching in COOH and CONH. It was observed that main peaks of Vildagliptin were present in mixture of drug and polymer, and no change in main peaks of drug IR spectra in a mixture of drug and polymers was found. Drug-Excipient compatibility studies by FTIR revealed no interaction between drug and the polymers used in the formulation thus showing compatibility

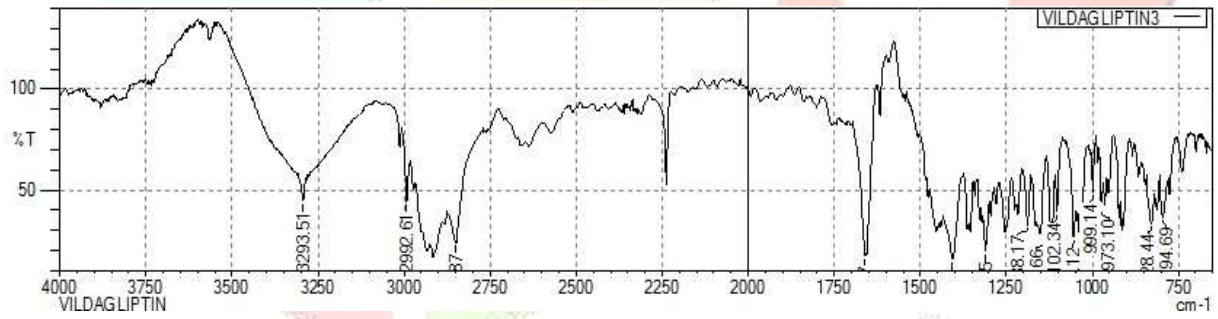

Figure 2: FTIR spectra of pure drug vildagliptin

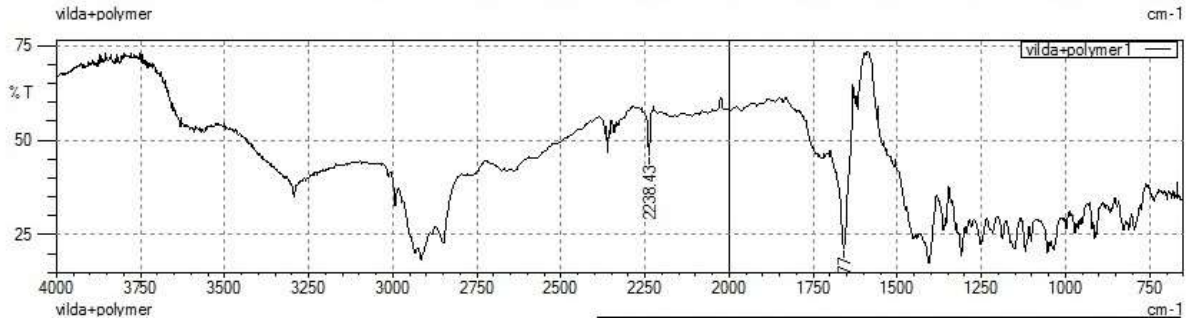

Figure3: FTIR spectra of vildagliptin and polymer

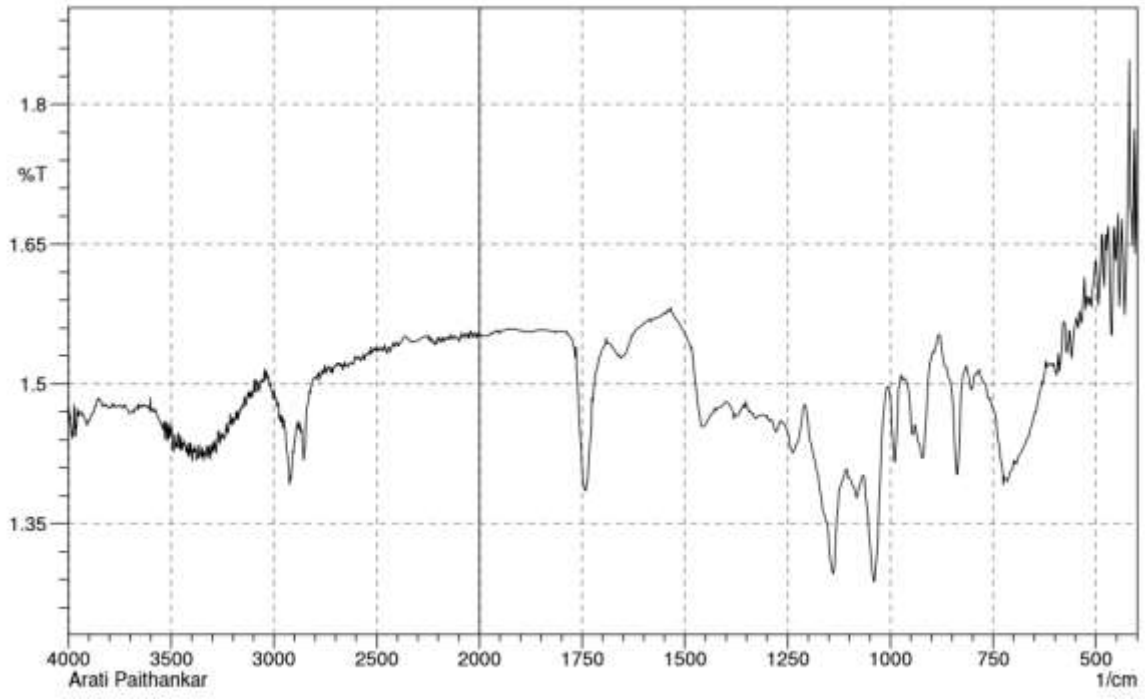

Figure4: FTIR spectra of Mixture

4.8 DSC study of Vildagliptin :

The purity of Vildagliptin drug was confirmed by comparison of the differential scanning calorimetry with the spectrum of the standard drug. Differential scanning calorimetry studied indicated a sharp endothermic peak at 153.60^{0}C for Vildagliptin.

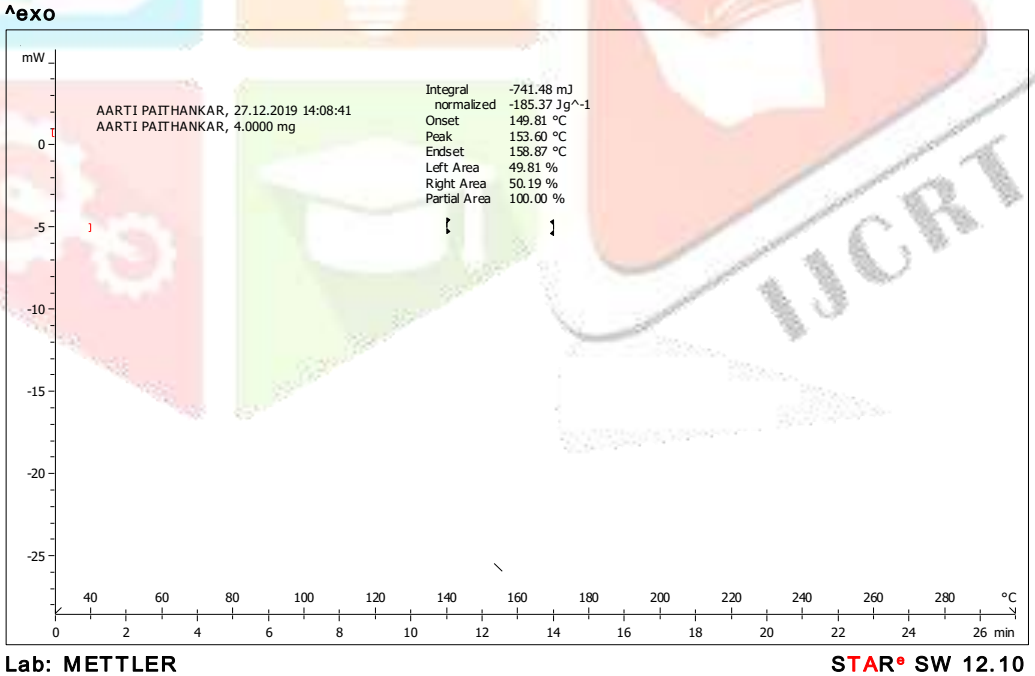

Figure 5: DSC spectrum of sample vildagliptin

4.9 Optimization:

Desirability values were calculated using Design-Expert® software for achieving optimal transdermal formulation by response surface analysis of the resultant data.The calculated desirability values were considered differentiating parameters for comparing the prepared transdermal formulaeA response surface study type with central composite design was employed to investigate the effect of independent variables on drug release pattern and folding endurance. This design was carried out with Design Expert 12 software to study the effect of concentrations of polymer(X_1), plasticizer(X_2) and permeation enhancer(X_3). The three independent factors were used at extreme point level for better results. As shown in Table 1.

4.10 In vitro drug release study:

In vitro drug release studies of Vildagliptin patch formulation through cellophane membrane showed slow and sustained release of drug up to 8h. The rank order of drug release from patch was found to be F9>F8>F7>F10>F15>F11>F13>F3>F1>F4>F14>F12>F5>F2>F6. The patch containing higher polymer concentration and plasticizer concentration 15%w/w of polymer showed maximum drug release. This study revealed that permeation enhancement effect of almond oil was due to interaction with intercellular protein to enhance penetration through corneocytes, and disruption of highly ordered structure of stratum corneum lipid with an increase intercellular diffusivity. The maximum drug penetrated across the skin with 3.68% almond oil as penetration enhancer. Aloe Vera gel powder and propylene glycol was used as polymer and plasticizer which has additional property of penetration enhancer that may result in enhancement of permeation and flux.

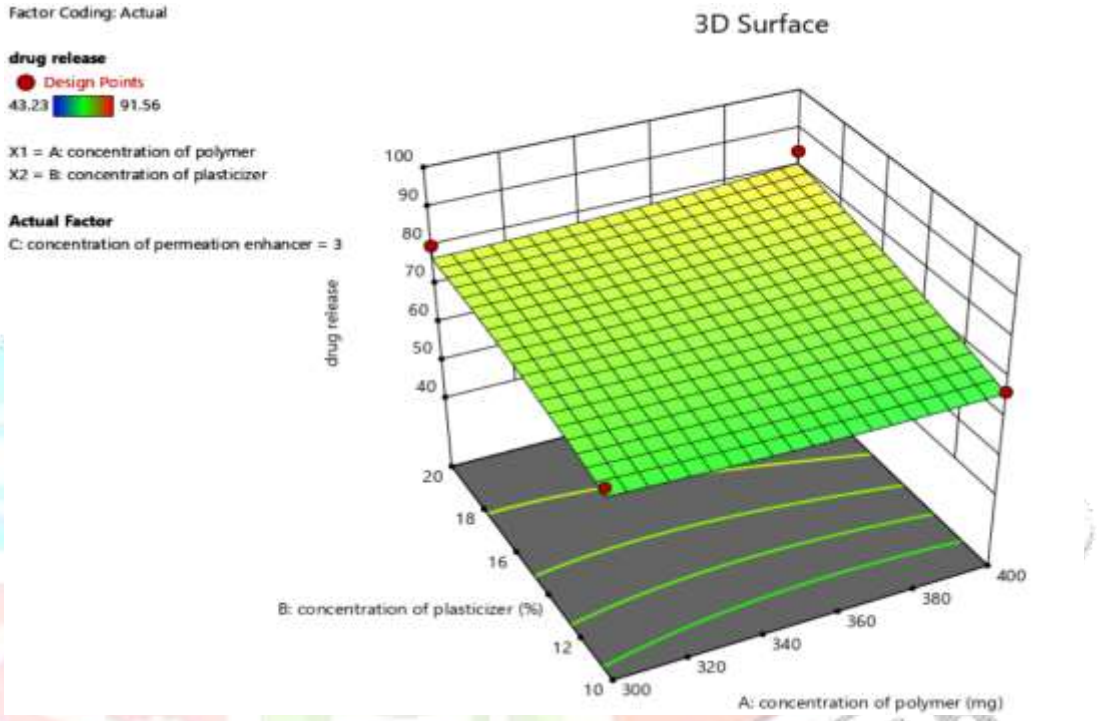

Figure 6: 3D response surface plot showing influence of polymer concentration, plasticizer concentration and permeation enhancer concentration on drug release

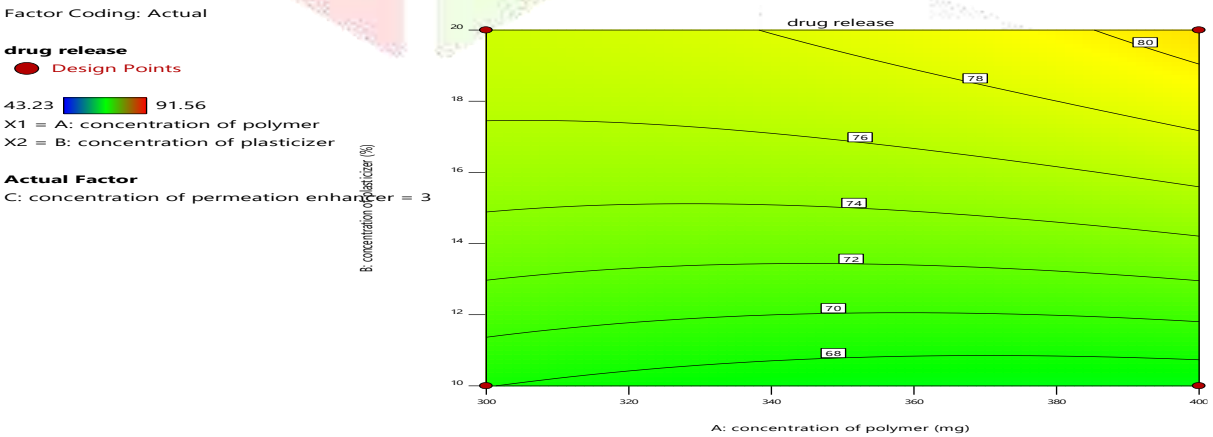

Figure 7: countur plot which shows effect of concentration of polymer, plasticizer and permeation enhancer on drug release

ANOVA analysis of the coefficients of the polynomial equations (eq.1) and the F- value 30.05 implied that the quadratic model is significant.

Drug release(Y_1) = +55.09+3.24A+1.54B+11.87C+1.28AB-2.70AC+4.33BC+0.6546 A^2-1.46 B^2+7.02 C^2.....(1)

In Eq.1 Y_1 denotes drug release while A is the concentration of Aloe Vera gel powder, B is the concentration of propylene glycol and C is the concentration of permeation enhancer. The graph reveals the contribution of aloe vera gel powder, plasticizer, and permeation

enhancer to drug release. As the concentration of Aloe vera gel powder increases drug release also increases, It is concluded that the concentration of aloe vera gel powder have direct relation with the Drug release.

The independent and response variable were related using polynomial equation with statistical analysis through Design-Expert software. The values of the coefficients X1 and X2 are related to the effect of these variables on the response. A positive sign of coefficient indicates a synergistic effect while a negative term indicates an antagonistic effect upon the response. The larger coefficient means the independent variable has more potent influence on the response.

4.11 Folding Endurance:

The data for all the formulations for folding endurance indicated that patch showing good patch properties. It is evident from the response surface plots that the folding endurance increases as the concentration of polymer decreases slightly (320mg) and plasticizer concentration increases. Polymer concentration also has an effect on folding endurance which can gives excellent flim properties. The reason behind use of plasticizer in transdermal patches for improvement of film forming properties and the appearance of the film. Propylene glycol may be forming hydrogen bonds with aloe Vera gel powder resulting in greater flexibility of patches at higher plasticizer concentration. And also it was found that high polymer concentration and low plasticizer concentration did not result in significant increases in folding endurance.

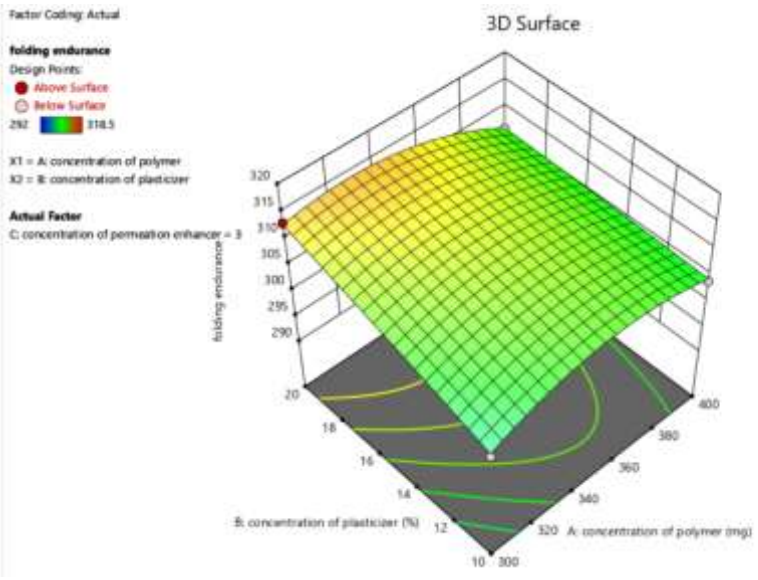

Figure 8: 3D response plot showing the effect of concentration of polymer, concentration of permeation enhancer, and concentration of plasticizer on folding endurance.

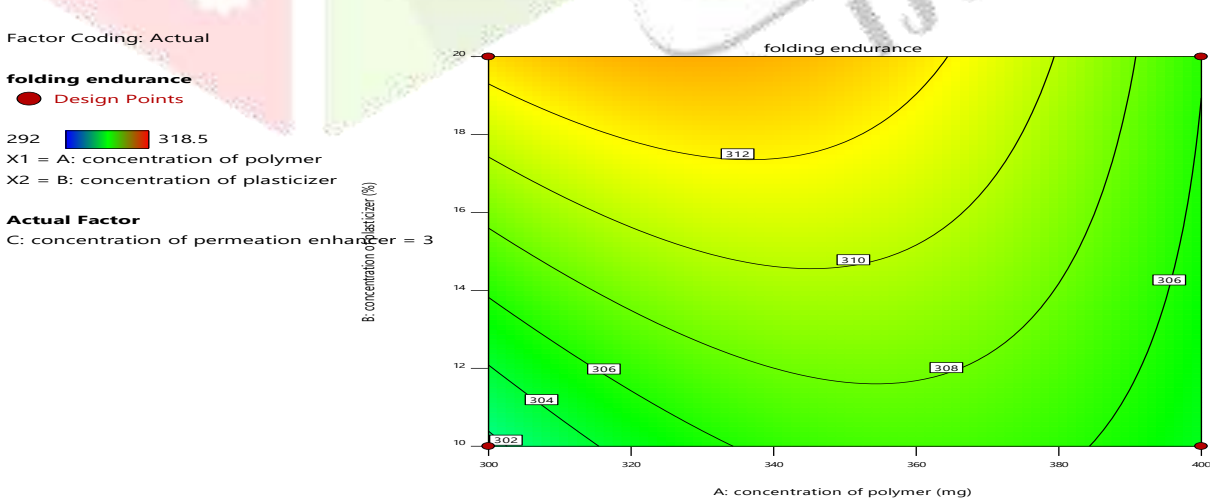

Figure 9: contour plot which shows effect of concentration polymer, plasticizer, and permeation enhancer on folding endurance

Coefficients of polynomial equations (eq2) and the model F- value of 45.99 implies model is significant.

Folding endurance= +304.96+0.6863 A+ 4.35 B+2.10 C-2.38 AB-1.63AC-1.13BC-3.86A^2-0.1983 B^2+3.20C^2 .....(2)

The graph reveals the contribution of Aloe Vera gel powder, propylene glycol, and almond oil to folding endurance. As the aloe vera gel powder increases slightly folding endurance decreases and folding endurance increases with increase in propylene glycol concentration. The equation in terms of coded factors can be used to make predictions about the response for given levels of each

factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

4.12 Evaluation of Transdermal patches

A. Thickness:

The prepared transdermal patches asper central composite design were, subjected to preliminary evaluation. All the patches were found to be very transparent, flexible and uniform in appearance. The thickness of patches was found to be in the range of 0.12±0.01 to 0.28±0.012mm thickness confirmed that the patches prepared were uniform in thickness.

B. Drug content:

The drug content was found to be in range of 93.03% to 99.12% indicated that the drug was uniformly dispersed in the polymeric matrix patch.

C. Surface pH:

The surface pH value of all patches was close to human skin pH is in the range 6.60 to 6.92 which means that there will be no skin irritation and therefore the patches will have good patient compliance as the patch was intended for once a day.

D.Percent Moisture content and Moisture uptake:

The moisture content in patches ranges from (2.3%w/w to 5.9%w/w). The moisture uptake in the formulations ranged from (1.02%w/w to 3.75%w/w) in a span of 24h. Moisture content is increased as the hydrophilic polymer concentration increased, Aloe vera gel powder is hydrophilic polymer. An increase in aloe vera gel powder content significantly increases the moisture content and moisture uptake. Moisture content and moisture uptake content was found to increase with increase in concentration of hydrophilic polymer and hydrophilic plasticizer (PG). Small % moisture content in all formulation is desirable as it helps films to remain stable and avoids formation to completely dried and brittle films. F11 has high moisture content and F2 has low moisture content as shown in fig 9

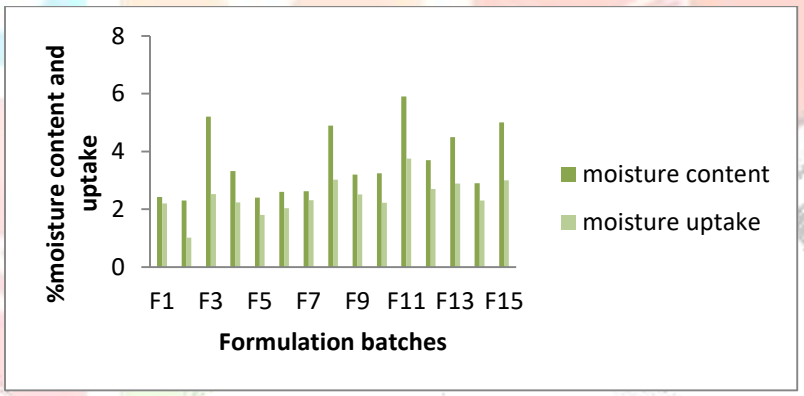

Figure 9: Moisture Content and Moisture uptake of transdermal patch

E. Stability Studies:

In order to determine the change in physicochemical parameter on storage, stability studies were carried out. Studies were carried out after storing the promising formulation (F9) at 40±2◦C temperature with 75±5% RH for 3 months. And showing data for Drug content, Appearance, folding endurance. The formulation F9 showed no change in appearance. And folding endurance. The drug content decreased from 99.12% to 98.85% after 90 days study

Time Period	Appearance	%Drug content	Folding Endurance
Initial	Pale White	99.12%	>300
After 3 months	Pale White	98.85%	>300

5. Conclusion:

Transdermal patch of Vildagliptin using Aloe vera gel powder as a rate controlling polymer, and Almond oil as a natural penetration enhancer were prepared and optimized using central composite statistical design. Patch containing higher concentration of polymer Aloe vera gel powder and plasticizer of 15%w/w of polymer propylene glycol showed maximum values of drug release, folding endurance because polymer and plasticizer having its hydrophilic nature. In vitro studies concluded that drug release from the patch containing Aloe vera gel powder as a polymer and Almond oil as penetration enhancer gives better results up to 10h.Hence present study demonstrate that natural polymer and natural permeation enhancer with medicinal values maybe successfully employed as a drug carrier and permeation enhancer for controlled and desirable drug delivery applications with additional health benefits.

6. Acknowledgements:

Authors would like to thank Alkem laboratories, Taloja, Mumbai, India for providing a gift sample of Vildagliptin and Mapple biotech. Pvt. ltd. Bhosri, Pune, India for providing a gift sample of Aloe Vera gel powder.

7. References:

[1] Anroop B Nair, Rachna Kumria, Bandar E Al-Dhubiab Development of Transdermal Delivery system of Vildagliptin and its Comparison with Oral Therapy. Indian journal of Pharmaceutical Education and Research, 2016;50(1):130-137

[2]Rao Monica, Sonavne Vijay, Kulkarni sayali, Magar M, Zope A, Karanjkar P, Design of transdermal patch of ketoprofen by full factorial design for treatment of rheumatoid arthritis. Journal of Drug Delivery and Therapeutics, 2019;9(2):197-205

[3]K. Subramanian,S. Narmada, U. Vishnupriya, and V. Vijaykumar, Release Characteristics of Aspirin and Paracetamol drugs from tablets with Aloe Vera gel powder as a drug carrier. Drug Invention Today,2010;2(9):424-428

[4]Kalpana Patle, Mithun Bhowmik, Jagdish Rathi, Formulation and Evaluation of Monolithic Matrix Transdermal Therapeutic System of Vildagliptin using polymers Eudragit RSPO and RLPO. International Journal of Medicine and Pharmaceutical Research,2018; 6(2): 50-61

[5]Nirav S, Girish J, Anil B, S.M. Vijayendraswami, Nishant U, Formulation, Evaluation and Optimization of Transdermal Drug Delivery System of Methotrexate using Different ratio of Eudragit RLPO/ RSPO. International Journal of Pharmacy Research and Technology,2012;2(2): 47-53.

[6] Gairola A, Chaurasia U, Singh A, Saharan VA. Development and Evaluation of Transdermal patches of aceclofenac. Journal of Pharmaceutical Sciences,2014; 38(2):90-7.

[7] Daleshwari Lohora, Kavita Attri, Manish Yadav, Preparation and Characterization of Transdermal Patches of Repaglinide for the treatment of Diabetes. SPER Journal of Pharmacy Research,2016;1(1):24-28.

[8] Vasantha PV, Mathew ST, Balaraman AK. Development and Characteristics of Eudragit based mucoadhesive buccal patches of salbutamol sulfate. Saudi Pharmaceutical Journal, 2011;19(4): 207-214

[9] Dey BK, Nath LK, Mohanti B, Bhowmik BB. Development and Evaluation of propranolol hydrochloride transdermal patches by using hydrophilic and hydrophobic polymer. Indian Journal of Pharmaceutical Education and Research, 2007;41(4):388-93

[10] Arun RR,Formulation Evaluation and invitro permeation studies of Transdermal nifedipine from matrix type patches. International Journal of Pharmacy and Pharmaceutical Sciences, 2014;6(1) 185-8

[11]Hadgraft J, Guy GH. Feasibility assessment in topical and transdermal delivery; mathematical models and in vitro studies. In Guy RH, Hadgraft J, editors, 2nd ed. New York; Marcel Dekker Inc.2003

[12] Tripathi KD, Singh J, Sakai TR. Effect of penetration enhancer on the in vitro transport of ephedrine through rat skin and human epidermis from matrix- based transdermal formulations. Drug Development and Industrial Pharmcy,1993;19(13):1623-8