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Formulation And Evaluation Of Topical Gel Of Vildagliptin Using Different Polymers.

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Abstract: Diabetes mellitus is a major global health issue that affects millions of people due to its harmful effects on mortality and overall health. It causes hyperglycemia and related problems and is characterised by abnormalities in insulin production and action, glucose metabolism, and insulin action.One especially common variant of diabetes mellitus that offers treatment and management issues is type 2 diabetes mellitus (T2DM). Among the available treatments, vildagliptin, a DPP-4 inhibitor, is unique in that it can regulate glucose metabolism by blocking the DPP-4 enzyme. Because it is non-invasive and doesn't cause gastrointestinal side effects, topical medication administration is a potential approach to managing diabetes. Gels are a good option for topical formulations because of their benefits as a dosage form, which include increased biocompatibility and enhanced drug release kinetics. The purpose of this study is to create a gel formulation containing vildagliptin that is stable, safe, and efficacious for topical administration. A range of polymers in varying concentrations will be assessed in order to maximise the formulation. Furthermore, the gel's stability and in-vitro performance will be evaluated. The goal of the research is to improve treatment results for patients with diabetes mellitus by reducing dosage frequency, increasing drug bioavailability, and mitigating hepatic first-pass metabolism by combining vildagliptin into a topical gel.

Keywords: Gel; Anti-Diabetic; Vildagliptin; Topical Drug Delivery; Evaluation tests.

1. INTRODUCTION:

1.1. Diabetes Mellitus:

Currently one of the most significant and expanding health issues in the world, diabetes mellitus is a key contributor to both early mortality and protracted illness [1]. Diabetes mellitus is a metabolic disease that is first characterised by a loss of glucose homeostasis and abnormalities in the metabolism of proteins, fats, and carbohydrates that are brought on by deficiencies in the action or production of insulin.The body's cells cannot properly absorb glucose from the blood if there is insufficient insulin in the body. Consequently, a rise in blood glucose levels is known as hyperglycemia [2,3]. When blood glucose levels are elevated, the pancreatic β-cells produce insulin to lower the level, while the α-cells release glucagon to raise the level by encouraging the production of glucose [4]. The hallmarks of type 2 diabetes mellitus (T2DM) include abnormal glucose

metabolism brought on by a decrease in pancreatic β cells, which are responsible for the typical symptoms of polyuria, polydipsia, and polyphagia [5,6].

There are quite a number of diseases that cause hyperglycemia continuing over a long period of time, known as Diabetes Mellitus. These diseases can be put into different categories because of the various ways they develop. [3]. Type I diabetes happens when the immune system attacks insulin-producing ß cells within islets of Langerhans leading to their inflammation or destruction which then brings this type about; while type II usually develops due to presence of insulin resistance all over the body tissues as well as having insufficient amount pancreas secreted hormone called insulin [4].

According to the International Diabetes Federation (IDF), 371 million individuals worldwide suffer with diabetes today, and 187 million of them are unaware that they have the disease. According to researchers, the diabetes problem will only become worse. They predict that 552 million individuals will have the illness by 2030 [2-3].

This disease can be controlled by following some dietary and exercising regimes and through insulin therapy and medical treatments by biguanides; sulfonylureas; alpha- glucoside inhibitors; meglitinidies; thiazolidinediones; and dipeptidyl peptidase inhibitors (DPP-IV).

1.2.Topical Gel:

Topical medication distribution is a desirable approach for both local and systemic therapy [15]. Topical drug delivery system (TDDS) is non-invasive, avoids first pass effect, and reduces GIT adverse effects, which makes it a promising alternative to oral administration [16]. A gel is a colloid, usually composed of 99% water, that is kept immobile by surface tension between it and a network of macromolecules made of a little amount of the gelating material that is present [17].

Compared to creams and ointments, gels frequently offer a quicker release of the drug's constituent ingredient, regardless of the drug's water solubility [18]. They are readily administered, do not require removal, and are extremely biocompatible with a reduced chance of inflammation or negative responses [19].

1.3. Introduction to vildagliptin:

Vildagliptin is a member of a family of DPP-4 inhibitors that use covalent bonds to temporarily alter the enzyme [7].The body's DPP-4 enzymatic activity is distributed throughout and plays a role in the immune system [8]. Vildagliptin is a strong, reversible, competitive inhibitor of DPP-4 that functions by binding to the protein's S1- and S2-catalytic sites and inhibiting its activity in two stages[9,10].Vildagliptin is hydrolyzed to produce its primary metabolite, LAY151, which is pharmacologically inert[11,12].Vildagliptin is absorbed quickly when taken orally. Vildagliptin undergoes hydrolysis for around 70% of its metabolism, renal excretion for 85%, and unaltered drug excretion in urine for 23% of the oral dosage. Consuming food has no effect on the drug's pharmacokinetics [13]. Age, gender, BMI, and race had no effect on the pharmacokinetics of vildagliptin [14].

2. MATERIALS AND METHODS:

2.1.Materials:

Vildagliptin Was purchased from Aarti Pharmaceuticals (Mumbai), Carbapol 940s was purchased from Loba chemie (Mumbai), Sodium alginate was purchased from Loba Chemie (Mumbai), Hydroxy propyl methyl cellulose was purchased from Pallav Chemicals & Solvents Pvt Ltd. (Mumbai), Methyl paraben was purchased from Thermosile fine chem industry (Mumbai), Propyl paraben was purchased from Molychem (Mumbai),

Propylene glycol was purchased from Loba Chemie (Mumbai).

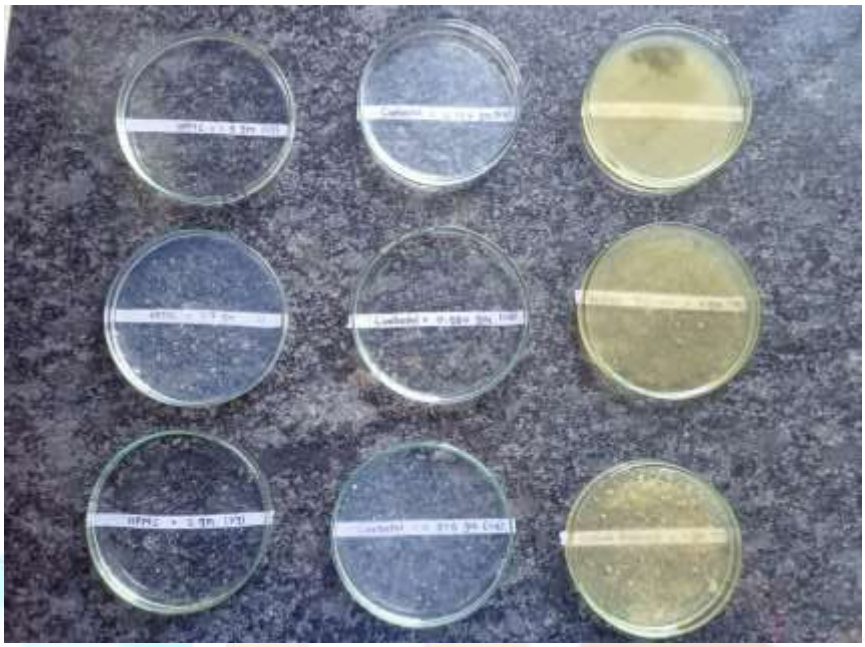


Figure No.1. Formulated batches

2.2.Procedure For formulating Gel:

For Formulations V1, V2, and V3, 1 g of vildagliptin was weighed and, with the use of some heat, dissolved in 15 ml of glycerin (solution A). The 75 millilitres of distilled water were mixed with a weighed quantity of HPMC and agitated until the HPMC was dissolved (solution B). After carefully combining Solutions A and B, the ultimate weight was increased to 100g.For Formulations V4, V5, and V6, 1g of vildagliptin was weighed and, using a little heat source , dissolved in 15ml of glycerine (solution B) A measured amount of carbapol 934P was mixed with 75 millilitres of distilled water, agitated until it was dissolved, and then 10% NaOH was added to neutralise the mixture (solution B).After carefully combining Solutions A and B, the total weight was brought to 100g. For Formulations V7, V8, and V9, 1g of vildagliptin was weighed, dissolved in 15ml of glycerin with the use of gentle heat, and then completely combined with methyl and propyl paraben.(solution A).75ml of distilled water was combined with a weighed quantity of sodium alginate, and the mixture was swirled to dissolve the alginate (solution B).After carefully combining Solutions A and B, the total weight was brought to 100g.

Table no.1. Concentration And Composition Of Vildagliptin Gel.

BATCH No.	Drug	Polymers(G)			10% Naoh	Glycerine	Methyl Paraben	Propyl Paraben	Distilled Water (Ml)
		Carbapol (G)	Sodium Alginate (G)	HPMC (G)					
V1	100mg	0.5	-	-	Q. S.	15	0.1	0.05	Upto100
V2	100mg	1	-	-	Q. S.	15	0.2	0.1	Upto100
V3	100mg	1.5	-	-	Q. S.	15	0.3	0.15	Upto100
V4	100mg	-	8	-	-	15	-	-	Upto100
V5	100mg	-	8	-	-	15	-	-	Upto100
V6	100mg	-	8	-	-	15	-	-	Upto100
V7	100mg	-	-	3	-	15	-	-	Upto100
V8	100mg	-	-	3.5	-	15	-	-	Upto100
V9	100mg	-	-	4	-	15	-	-	Upto100

6. Experimental work:

6.1.Preformulation studies:

To guarantee the creation of a stable, therapeutically effective, and safe dosage form, preformulation studies are required.

6.1.1. Melting Point:

Apply heat to one end of a capillary tube and rotate it constantly for two to three minutes to shut the tube. Use finely powdered vildagliptin. Dip the capillary tube's open end into the finely ground Vildagliptin. To fill the capillary tube with compound to a length of approximately 1-2 cm, gently tap it on the table. Put the capillary tube with the powdered vildagliptin inside the melting point device. To measure the sample's temperature precisely, make sure the thermometer is positioned appropriately. Gradually raise the sample's temperature and record the point at which it begins to melt. Note the temperature range between the sample's beginning to melt and its complete liquid state.

6.1.2. Fourier transform infrared spectroscopy (FT-IR):

The pure drug sample was identified analytically using the FTIR spectrum. Using the KBr pellet approach, the spectra of the material were recorded using a Bruker Vertex 70 FTIR spectrophotometer. The samples were individually mixed with potassium bromide (1:10) for analysis, and then pressure was applied using a KBr press to produce a thin pellet. The sample holder was filled with the produced pellets. A spectral scan was conducted within the wavelength range of 4000-400 cm−1. Vildagliptin FTIR scans were taken and recorded.

6.1.3. Drug excipients Compatibility study:

The Fourier Transform Infrared Spectrometry (FTIS) method was employed in testing drug 39xcipients compatibility using Bruker Alpha II spectrophotometer, ranging from 4000 to 400 cm^-1. For analysis purpose,

a drug and polymer were mixed before putting onto the sample holder whereby it became solid to facilitate analysis.

6.2. Spectroscopical analysis:

6.2.1. Determination of Lambda max by UV Spectroscopy:

Vildagliptin lambda max was calculated by dissolving 10 mg of the medication in 100 ml of distilled water, then diluting the solution to create a strength of 100 µg/ml using the same solvent. The maximum wavelength was then ascertained by scanning it in the 400–200 nm range with distilled water serving as a blank using a UV–visible spectrophotometer (Shimadzu UV-1900i UV–Vis Spectrophotometer).

6.2.2. Preparation of Calibration curve*:*

Calibration curve of Vildagliptin was prepared with the help of UV spectroscopy. Calibration curve of Vildagliptin was prepared in distilled water.

6.3. Calibration curve:

6.3.1. Preparation of stock solution:

Vildagliptin (10 mg) was precisely weighed and added to a 100 ml volumetric flask. A solution containing 100 µg/ml was obtained by dissolving the medication and diluting it with water until it reached the desired level.

6.3.2. Preparation of working solution:

A precise 10 ml volumetric flask was used to extract appropriate aliquots (0.2, 0.4, 0.6, 0.8, 1, and 1.2 ml) from the vildagliptin stock solution. The final concentration of the solution was diluted with water until it reached the desired range of 2–12 µg/ml, and it was then scanned at Lambda max. Using water as a blank, the absorbance of various vildagliptin solutions was measured at their Lambda maximum.

6.4.Evaluation of Vildagliptin Gel:

6.4.1. pH:

A digital pH metre was used to measure the pH of several gel compositions.

6.4.2. Spreadability:

A wooden block and a glass slide contraption were used to determine it. About 20g of weight was added to the pan, and the amount of time it took for the moveable upper slide to fully separate from the fixed slides was recorded [20].

Spreadability was then calculated by using the formula:

$$S = M.L/T$$

Where,

S = Spreadability

M = Weight tide to upper slide

L = Length of glass slide

T = Time taken to separate the slide completely from each other.

6.4.3. Viscosity:

A Brookfield viscometer was used to measure viscosity. Using a Brookfield viscometer, viscosity measurements were made at ambient temperature (25–27°C) [21].

6.4.4. Homogeneity

After the gels were placed in the container, a visual inspection was used to verify that all of the generated gels were homogenous. Their appearance and the existence of any aggregates were examined [22].

6.4.5. Skin irritation test

A human volunteer population was used to test for irritation. Five participants were chosen for each gel, and 1.0g of the prepared gel was applied to the back of the hand in a 2 square inch region. We looked for sores or irritation on the participants.

6.4.6. Permeability studies:

The receptor media for in vitro release was phosphate buffer with a pH of 6.8. In the Franz diffusion cell, the eggshell's outer membrane was utilised. The gel sample was placed on the egg membrane and fastened between

the diffusion cell's donor and receptor compartments. The receptor compartment contained phosphate buffer (100ml) of pH 6.8.The temperature of diffusion medium was thermostatically controlled at 37º C ± 1ºC by surrounding water in jacket and the medium was stirred by magnetic stirrer at 600rpm. The sample at predetermined intervals were withdrawn and replaced by equal volume of fresh fluid. The samples withdrawn were spectrophotometrically estimated at 213 nm against their respective blank.

RESULTS AND DISCUSSION:

6.5. Preformulation studies:

6.5.1. Melting point:

The reported melting point of vildagliptin was in the range of 149^0C-155^0C. The observed melting point of the was found at 152^oC by using Thieles tube method. It confirms that the given powdered drug is pure in nature and it complies that powder is vildagliptin.

Drug	Melting point	Observed melting point
Vildagliptin	149^0C-155^0C	152^0C

Table No. 2. Melting Point of Drug

6.5.2. FT-IR:

IR spectra from the vildagliptin, sodium alginate, Carbapol 940s, Hydroxy propyl methyl cellulose are shown as following.

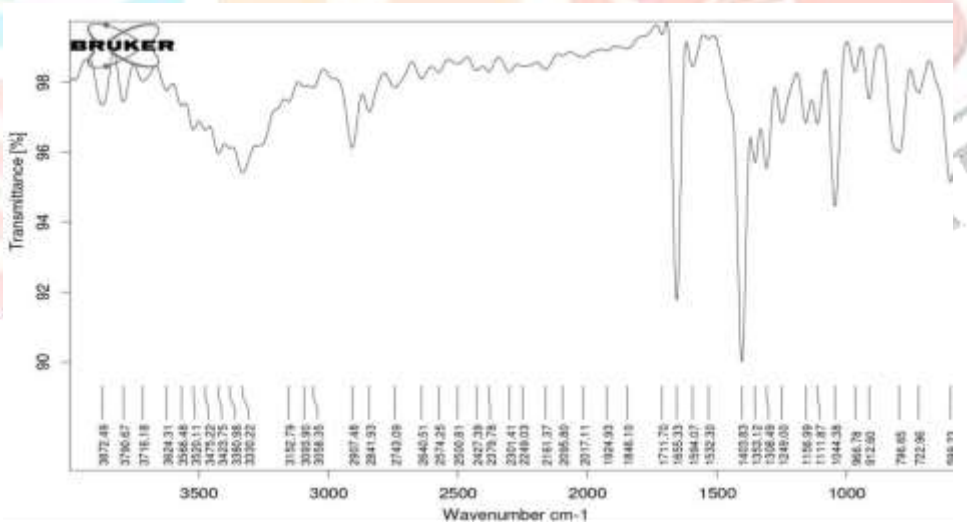


Figure No. 2. I.R. Spectra of Vildagliptin

The infrared (IR) spectrum reveals characteristic absorption bands for various functional groups. Carbonyl (C=O) stretching appears around 1650-1655 cm^{-1}. Alcohols exhibit broad O-H stretching from 3200-2700 cm^{-1}, though the 2907.48 cm^{-1} peak is likely C-H stretching. Amine salts show N-H stretching in the 3000-2800 cm^{-1} range, with 2841.93 cm^{-1} probably corresponding to C-H stretching.The IR spectrum provides distinct peaks for various functional groups. Tertiary alcohols show C-O stretching vibrations between 1205-1124 cm^{-1}, with a peak at 1141.28 cm^{-1}. Conjugated alkenes have C=C stretching bands in the 1650-1600 cm^{-1} range, with a notable peak at 1611.36 cm^{-1}, indicating the presence of conjugated double bonds.The IR spectrum for a primary alcohol shows C-O stretching vibrations within the range of 1085-1050 cm^{-1}, with a specific peak at 1070 cm^{-1}. This peak confirms the presence of the C-O bond characteristic of primary alcohols.

The IR spectrum identifies specific functional groups by their characteristic absorption bands. The hydroxy group shows O-H stretching in the range of 3500-3400 cm^{-1} with a peak at 3419.0 cm^{-1}. Alkanes display C-H stretching between 3000-2840 cm^{-1}, with a peak at 2901.4 cm^{-1}. Carboxylic acids exhibit C=O stretching in the 1740-1720 cm^{-1} range, with a peak at 1737.0 cm^{-1}.

6.5.3. Drug-excipients compatibility study:

Drug-excipients compatibility study was done by using FT-IR spectra, from this graph it was prove that there is no change in the IR spectra of physical mixture of drug and excipients.

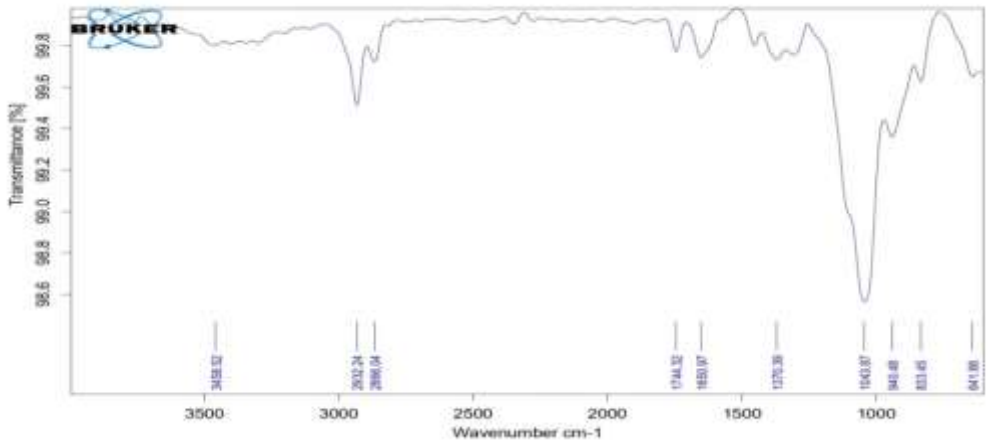
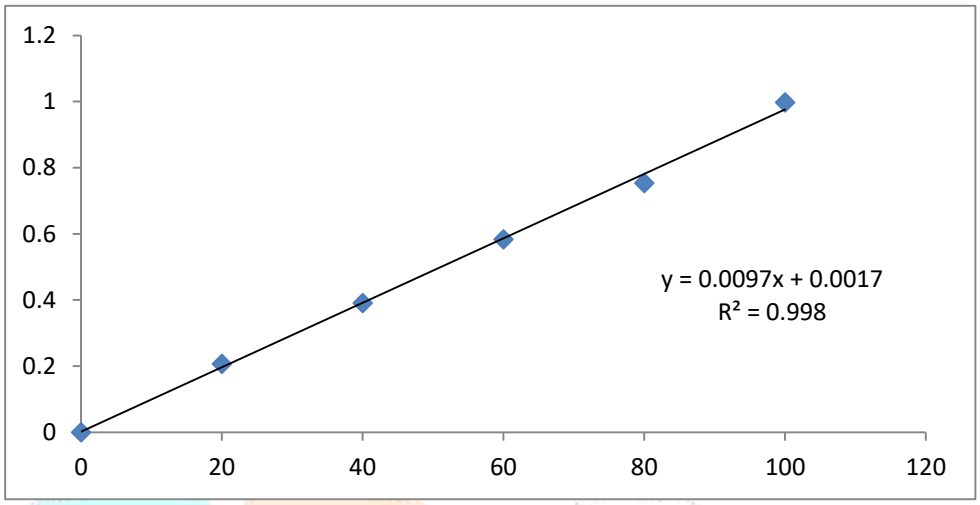


Figure .No. 3. I.R. Spectra of Physical Mixture.

6.6.Spectroscopic studies:

6.6.1. Determination of Lambda max by UV Spectroscopy:

The absorption spectrum of vildagliptin was acquired from a solution of 100 µg/ml concentration in distilled water, revealing an absorbance peak at 213 nm.



6.7.Calibration Curve of vildagliptin in Distilled Water:

The graph of Concentration Vs Absorbance for pure Vildagliptin was found to be in the concentration of range 2-10 µg/ml.

Table No. 3. Calibration Curve Of vildagliptin in Distilled Water

Concentration (µg/ml)	Absorbance
0	0
2	0.207
4	0.391
6	0.583
8	0.754

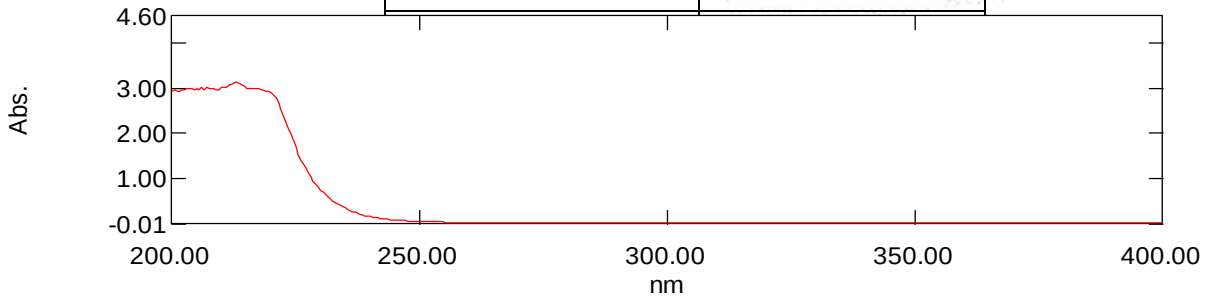


Figure No. 5. Calibration curve of vildagliptin in distilled water

Table No. 4. Various constant for Calibration Curve Of vildagliptin in distilled water.

Parameter	slope	intercept	R^2
Value for calibration curve in Vildagliptin	0.009	0.001	0.998

6.8.Characterization of Vildagliptin:

6.8.1. pH:

The pH values of all developed formulae was in range 6-7 which is considered acceptable to avoid the risk of irritation upon application to the skin.

6.8.2. Spreadability:

The spreadability is very much important as show the behavior of gel comes out from the tube. The values of spreadability shown in table (2) indicate that all the polymers used gave gels spread by small amount of shear. The diameters of the spreaded circles ranged from 3 cm seen with the Pluronic F127gel and 5 cm seen with carbopol and HPMC gel. Data in table (2) revealed that increasing the concentration of any of the gelling agents was always associated with a decrease in the spreadability as expressed by the lower diameter of the spreaded circle.

Table No. 4. Results obtained for various studies.

Formulations	pH	Spreadabilit (g.cm/sec)	Viscosity (m.pa)	Homogeneity
V1	6.88 ± 0.08	4.84 ± 0.34	320.0 ± 1.29	Homogeneous
V2	**6.97** ± 0.02	**5.79** ± 0.26	**371.5** ± 1.78	Homogeneous
V3	6.70 ± 0.07	4.29 ± 0.38	310.8 ± 1.56	Homogeneous
V4	6.67 ± 0.06	2.80 ± 0.18	365 ± 1.09	Homogeneous
V5	6.76 ±0.10	2.90 ± 0.25	370.0 ± 1.76	Homogeneous
V6	**6.94** ± 0.3	**3.07** ± 0.33	**417.9** ± 0.87	Homogeneous
V7	6.59 ± 0.5	4.3 ± 0.12	413.8 ± 1.13	Homogeneous
V8	**6.82** ± 0.4	**5.9** ± 0.23	**454.13** ± 1.47	Homogeneous
V9	6.71 ± 0.4	5.2 ± 0.29	305.9 ± 1.15	Homogeneous

6.8.3. Viscosity:

Viscosity measurement of all the formulations revealed optimum consistency and the results are reported in table no.

6.8.4. Homogeneity:

All developed creams were tested for homogeneity by visual inspection after the creams have beenset in the container.

6.8.5. Skin irritation:

The skin irritation studies of developed gel were carried out on human volunteers and that confirmed the absence of any irritation on the applied surface in all formulations.

6.8.6. Permeability studies:

Table No. 16. Drug release of formulations:

Time (hr)	% Drug Release								
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
0	0	0	0	0	0	0	0	0	0
30.	19.14 ± 1.34	18.92 ± 1.05	19.11 ± 1.12	19.62 ± 0.71	17.58 ± 0.83	19.20 ± 0.80	18.78 ± 0.81	18.81 ± 0.89	18.29 ± 0.82
60.	29.89 ± 0.77	27.26 ± 1.16	28.27 ± 0.94	29.22 ± 0.92	27.52 ± 0.99	25.85 ± 0.76	26.92 ±0.78	25.32 ± 0.91	35.62 ± 0.65
90.	35.43 ± 0.96	38.29 ± 0.87	33.16 ± 0.81	34.35 ± 1.21	30.07 ± 0.78	35.52 ± 0.62	32.14 ± 0.64	36.92 ± 0.66	39.56 ± 0.59
120.	43.03 ± 0.88	55.91 ± 0.93	44.62 ± 0.54	50.09 ± 0.87	40.24 ± 1.13	52.32 ± 0.73	43.69 ± 0.87	52.58 ± 0.88	49.78 ± 0.87
150.	59.99 ± 1.13	74.31 ± 0.66	54.86 ± 0.86	64.65 ± 1.04	55.01 ± 0.90	64.30 ± 0.78	51.43 ± 1.06	62.28 ± 0.75	64.86 ± 0.93
180	63.48 ± 0.76	78.99 ± 82	61.94 ± 0.99	69.95 ± 0.83	63.32 ± 0.88	78.11 ± 0.71	58.3 ± 0.67	72.29 ± 69	69.75 ± 0.78
210	75.39 ± 1.02	**90.78 ± 0.79**	84.64 ± 0.93	77.82 ±0.88	89.54 ± 0.66	**89.06 ± 0.91**	82.2 ±0.77	**91.94 ± 1.09**	87.79 ± 0.69

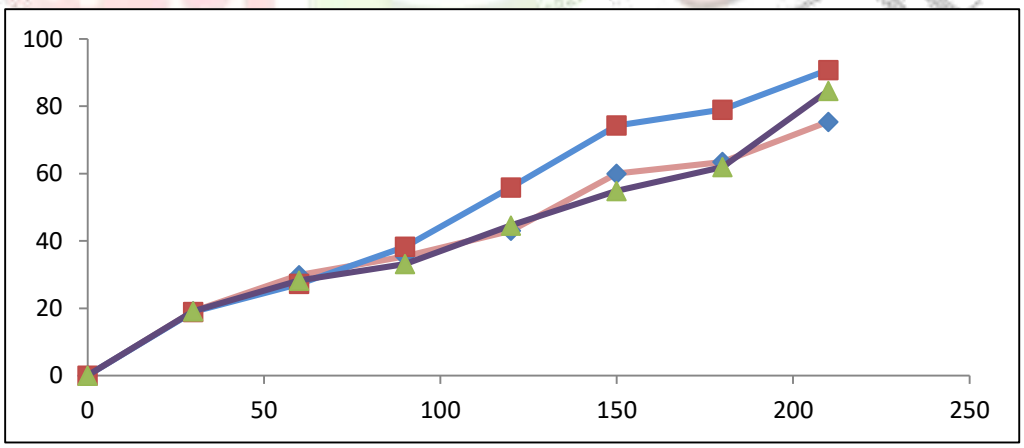


Figure No. 6. drug release of formulation V1, V2 and V3.

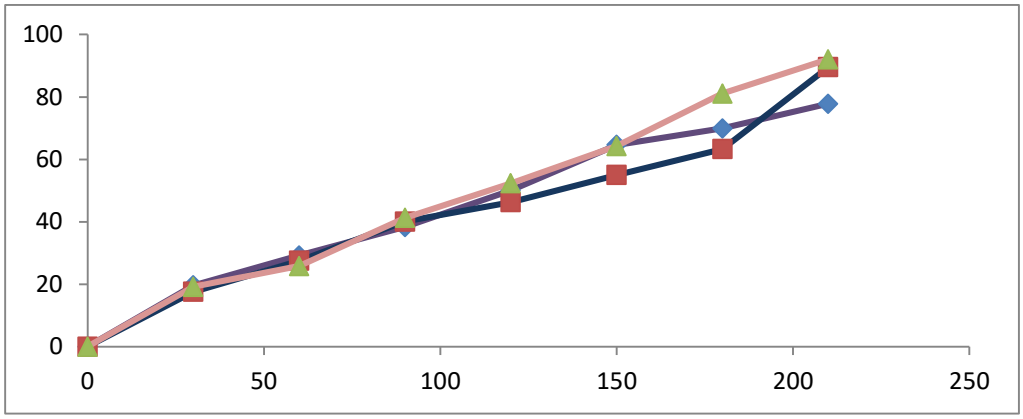


Figure No. 7. Drug release of formulations V4, V5 and V6.

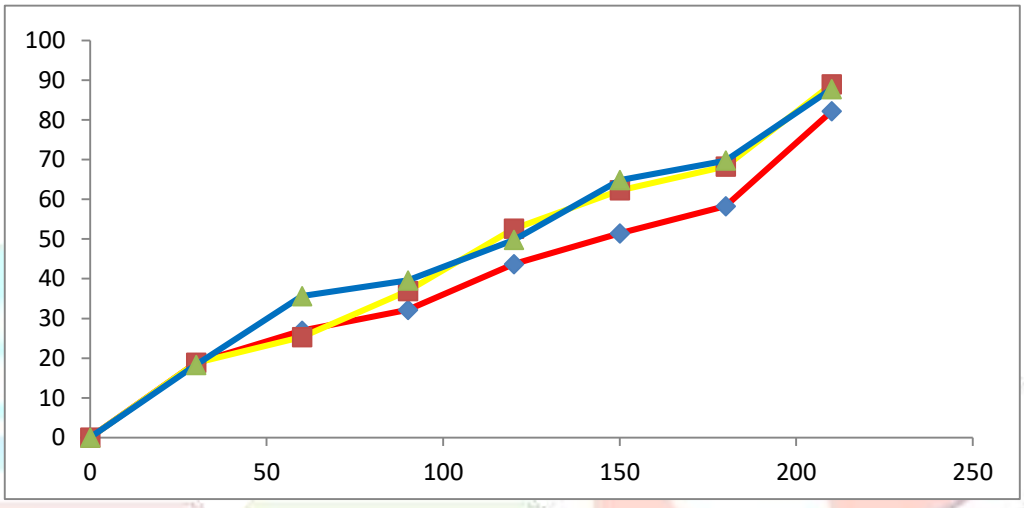


Figure No. 8. Drug release of formulations V7, V8 and V9.

7. Conclusion:

In conclusion, the development and evaluation of a Vildagliptin gel formulation provide a comprehensive approach to enhancing the management of type II diabetes mellitus. Vildagliptin, a DPP-4 inhibitor, shows efficacy in lowering blood glucose levels by inhibiting the enzyme responsible for degrading incretin hormones, thereby increasing insulin secretion and decreasing glucagon release. With its rapid absorption, a bioavailability of 85%, and a half-life conducive to manageable dosing, Vildagliptin stands as a potent anti-diabetic agent.

The formulation of Vildagliptin gel involved using various excipients, including Carbopol, sodium alginate, and Hydroxy Propyl Methyl Cellulose (HPMC). These excipients were selected for their roles as thickeners, emulsifiers, and agents that improve the stability and release of the drug. Preformulation studies, such as determining the melting point, performing FT-IR spectroscopy, and establishing a calibration curve via UV spectroscopy, confirmed the drug's purity and compatibility with the selected excipients.

Experimental results highlighted the successful preparation of multiple Vildagliptin gel batches with varying polymer concentrations. Characterization of the formulations revealed desirable properties: pH values within a safe range (6-7), adequate spreadability, and optimal viscosity for easy application. Furthermore, homogeneity tests ensured the consistency of the gels, and skin irritation tests confirmed their safety for topical use.

The permeability studies indicated effective drug release from the gel formulations, particularly from formulation V2, which demonstrated superior spreadability and consistent viscosity. These findings support the feasibility of using Vildagliptin gel as an effective, user-friendly treatment for type II diabetes, combining

therapeutic efficacy with enhanced patient compliance through topical administration.

It was observed that hydroxy propyl methylcellulose (HPMC) gel containing Vildagliptin (V8) produced better Spreadability and consistency as compared to carbapol 934P gel (V2) and sodiumbalginate gel (V6) formulation. The developed V8 gel showed good homogeneity, no skin irritation, good stability and *in vitro* permeability. The HPMC forms water washable gel because of its water solubility and has wider prospects to be used as a topical drug delivery system.

8. Acknowledgement:

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9. Conflict of Interest Statement:

The authors declare that they have no conflicts of interest regarding the publication of this review paper. All authors certify that they have no financial or personal relationships with other people or organizations that could inappropriately influence (bias) their work or this manuscript.

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