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Formulation and evaluation of transdermal patch of vildagliptin

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Abstract

Objective: In the present research, the transdermal patch of vildagliptin was fabricated by using sustained release hydrophilic and lipophilic polymers containing permeation enhancer and thoroughly evaluated.

Methods: The transdermal patches of vildagliptin were prepared using the combination of polymers in different concentration with permeation enhancer and plasticizer was used for the formulating transdermal drug delivery system. The thickness, folding endurance, tensile strength, percentage of moisture content, percentage of moisture uptake, drug content analysis, scanning electron morphology (SEM) was evaluated.

Results: All the formulation was studied and all data fitted on zero order and first order, to explain the diffusion mechanism and pattern. The % cumulative drug release was calculated over the study time range in 0-10 h. 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 F3 was to be found higher as compared to other formulation.

Conclusion: The preparation of matrix type transdermal patch appears to be a most effective approach from the process development and scale-up point of view.

Keywords: Transdermal patch, Vildagliptin, Polymers, Permeation enhancer, Plasticizer, Transdermal drug delivery system

Introduction

A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication. These devices allow pharmaceuticals to be delivered across the skin barrier [1]. A drug is applied in a relatively high dosage to the inside of a patch, which is worn on the skin for an extended period of time. Through a diffusion process, the drug enters the bloodstream directly through the skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow. The best mixture is about fifty percent of the drug being each hydrophilic and lipophillic. This is because "Lipid-soluble substances readily pass through the intercellular lipid bi-layers of the cell membranes whereas water-soluble drugs are able to pass limiting steps in transdermal drug delivery system. Sweat ducts and hair follicles are paths of entry, but they are considered rather insignificant [2].

Vildagliptin possesses distinct physicochemical properties such as poor water solubility, small molecular mass and reason-able melting point which suggest its prospects to be delivered through the skin. Formulating a transdermal drug delivery product of this drug is likely to overcome the hepatic adverse effects and could maintain proper blood level for a prolonged period of time, which in turn would overcome the biopharmaceutical limitations that prevent the successful delivery of vildagliptin in oral therapy [3]. Extensive studies are being carried out to develop an alternative system which can surmount the existing issues and provide controlled and effective delivery of vildagliptin. Therefore in the present investigation, six different formulations were formulated using different concentration of vildagliptin, polemer, permeation enhancer and plasticizer by solvent evaporation technique. The transdermal patches were evaluated for their physic chemical characteristics such as thickness, weight variation, tensile strength, folding endurance, content uniformity, permeability characteristics and stability studies.

Materials and methods

Drug and excipients

Vildagliptin was purchased from Nacto Pharma, Hyderabad, HPMC from Ozone International, Eudragit RLPO and Eudragit RSPO from Evonik Rochm Pharma Polymers, Ethyl cellulose from S.D. Fine Chemicals, PEG 600 from Thomas Baker Chemicals Pvt Ltd., Chloroform from Himedia Lab Pvt Ltd. Mumbai, Methanol from Lobacheme Laboratories and Glycerin was purchased from Wallis Pharmaceuticals.

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Instruments

Double beam UV visible spectrometer of Labinida 3000+, FTIR 200 Spectrometer of Brucker Alpha, Electronic balance of Wensar PGB 200, Karl Fischer apparatus of Chemilab CL510, pH meter of Electronic India, Melting point apparatus of Chemline, Vortex mixture of Ultra Lab was used for the study.

Preformulation studies

The objective of preformulation study was to get generic information useful to the formulater in developing stable and bioavailable dosage form. The use of preformulation parameter maximizes the chances in formulation an acceptable, safe, efficacious and stable product and at the same time provides the basis for optimization of the drug product quality. The preformulation studies were carried out in terms of testa for identification (physical appearance, melting point, spectrophotometer and FTIR spectroscopy), solubility profile, and compatibility studies of drug with excipients [4].

Formulation development

Accurately weighed polymers were taken in combination and dissolved in respective solvent (chloroform and methanol) then poured in petridish with glycerin on plain surface. Then film was dry over night at room temperature. HPMC and ethyl cellulose were used for the preparation of rate controlling membranes. Polymers were dissolved in chloroform and methanol with PEG-600 as plasticizer. Then solution was then poured into a glass Petri dish. The solvent was allowed to evaporate under room temperature for 24 h. The polymers HPMC, ethyl cellulose were dissolved in chloroform and methanol along with plasticizer. Then the solution was poured into a glass Petri dish containing glycerin. The solvent was allowed to evaporate under room temperature for 24 h. The polymers (total weight: 400 mg) and drug (10 mg) were weighed in requisite ratios and dissolved in 10 ml of chloroform and methanol and PEG 400. After vortex then the solution was poured on glycerin placed in a glass Petri dish and dried at room temperature for 24 h. The patch was obtained intact by slowly lifting from the Petri dish and transdermal patches were cut into radius of 2 cm^2 [5-7].

Table 1: Different formulation used for optimization TDDS

Formulation Code	Drug (mg)	HPMC (mg)	Ethyl cellulose (mg)	Total polymer weight (mg)	Plasticizer % w/w	Permeation Enhancer % w/w
F1	10	375	25	400	0.5	10
F2	10	350	50	400	0.5	10
F3	10	325	75	400	0.5	10
F4	10	300	100	400	0.5	10
F5	10	275	125	400	0.5	10
F6	10	250	150	400	0.5	10

Tensile strength

Tensile strength of the patches was determined on tensile strength testing apparatus. Rectangular patch strips of 2 cm length and 2 cm breadth were fixed between the jaws of the instrument. The load on the strip was gradually increased to a maximum at a speed of 50mm/min and the change in the length of the strips that occurred with increasing stress was measured [8].

Folding endurance

A patch of 2 cm radius (4 cm diameter) was cut evenly and repeatedly folded at the same place till it brakes. The numbers of times the film was folded at the same place without breaking give the value of the folding endurance [9, 10].

Percentage moisture content

The prepared films were weighed individually and kept in a desiccators containing fuse calcium chloride at room temperature for 24 h. After 24 h, the films were reweighed and determined the percentage moisture content from the mentioned formula [11, 12].

Percentage moisture uptake

The weighed films were kept in desiccators at room temperature for 24 h containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 h, the films were reweighed and determined the percentage moisture uptake from the below mentioned formula [13, 14].

Drug content

A specified area of patch was dissolved in a phosphate buffer solution. The content was stirred to dissolve the film. The content was transferred to a volumetric flask. The absorbance of the solution was measured at wavelength 284 nm and determines the drug content [15].

Scanning electron morphology (SEM)

SEM study help to investigate the surface morphology of patch. 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).

Kinetic analysis of data

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To analyze the in vitro release data various kinetic models were used to describe the release kinetics. The zero order rate describes the systems where the drug release rate is independent of its concentration .The first order describes the release from system where release rate is concentration dependent. Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion [16, 17].

In vitro diffusion cell study

The diffusion study was performed using Franz's diffusion cells to determine the permeability of the drug through the barrier of the fabricated transdermal system. The egg membrane was separated and used for *in vitro* study. In the experiment protocol, the egg membrane was placed in the receptor compartment and both compartments were held tight by the clamps. The phosphate buffer of pH 7.4 was employed as the receptor solution. The volume of diffusion cell was maintained 6 ml throughout the study and stirring was continued at 100 rpm with the magnetic bead. The temperature of the whole system was maintained at 37 °C ± 1 °C with the help of the hot plate. The diffusion study was carried out for the period of 12 h where 1 ml sample was withdrawn cautiously at every 1 h interval and analyzed at 335 nm, spectrophotometrically. The same volume of phosphate buffer (pH 7.4) was added to the receptor compartment to maintain the sink condition [18].

Results and discussion

Preformulation studies

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.

Table 2: List of sensory characters

S. No.	Sensory characters	Results
1.	Taste	Tasteless
2.	Appearance	White to off-white
3.	Odor	Odorless
4.	Texture	Crystalline

Table 3: 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 (-)

Table 4: Melting point of 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	

Table 5: pH of vildagliptin

S. No	pH of solution	Average pH of solution
1.	7.7	7.73±0.057
2.	7.7	
3.	7.8	

*(n=3±SD)

Solubility study of vildagliptin has been done in various solvent such as water, ethanol, methanol, acetone 0.1N NaOH and 0.1N NaOH solution. We were found that a solubility of vildagliptin was good in water, ethanol, methanol, 0.1N HCl solution and poorly soluble in 0.1N NaOH and chloroform. Melting point was determined by melting point apparatus at 152-153 ºC. The high melting point of drug was important for its sustained release floating property of tablets. The pH determination of vildagliptin was done by digital pH meter and found to be 7.73±0.057. It means the drug was

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very weak acidic in nature. 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. The percentage of loss on drying was found to be 1.672 %. It means drug was free flowing in nature. 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. 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. 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.

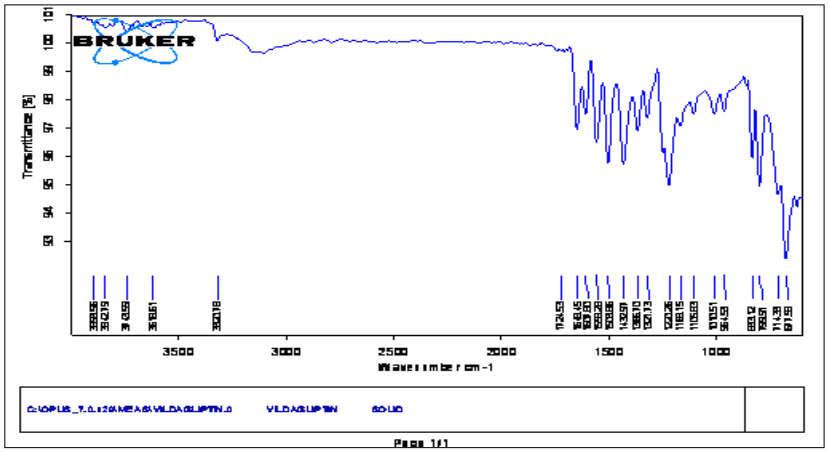

Figure 1: FTIR Spectrum of pure drug (Vildagliptin)

Table 6: Loss of drying of drug sample

S. No.	Initial weight	Final weight after 5 min	% loss on drying	Avg. % loss on drying
1.	5 gm	4.98 gm	0.40%	0.047±0.115
2.	5 gm	4.97 gm	0.60%	
3.	5 gm	4.98 gm	0.40%	

*(n=3±SD)

Table 7: Tapped density of vildagliptin

S. No.	Bulk mass	Tapped volume	Tapped density	Avg. tapped density
1.	5 gm	10.5 ml	0.476 g/ml	0.470±0.067 g/ml
2.	5 gm	10.7 ml	0.467 g/ml	
3.	5 gm	10.8 ml	0.463 g/ml	

*(n=3±SD)

Table 8: Hausner of vildagliptin

S. No.	Bulk density	Tapped density	Hausner ratio
1.	0.450±0.006	0.470±0.067	0.957

Table 9: Moisture content determination

S. No.	Drug	KF Factor	Amount of KF Reagent consumed	Moisture content
1	Vildagliptin	0.555	0.12ml	0.066

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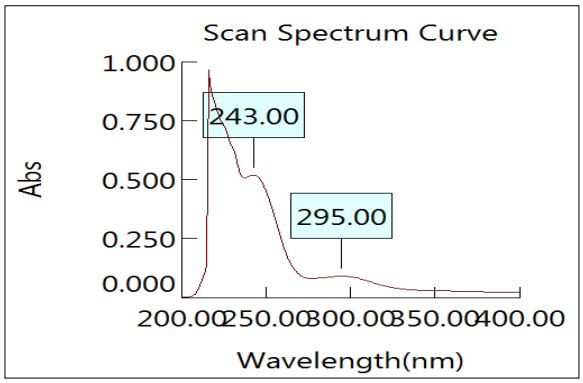

Figure 2: Standard calibration curve of vildagliptin

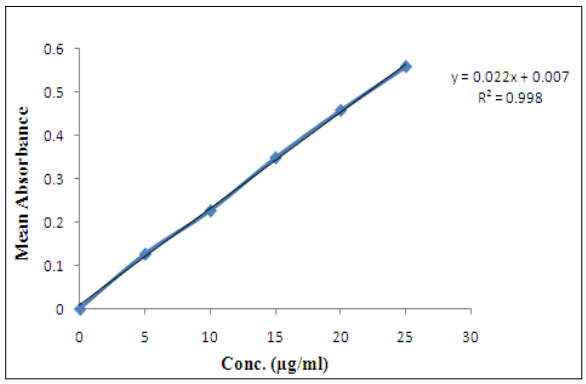

Figure 3: The linear regression analysis for standard curve

Table 10: 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

From the UV and 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. The FTIR study shows that the drug and excipient are compatible with each other. 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, F-1 was found to be most appropriate in all formulation. The thickness of the patch varied from 78±2 to 92±8 mm. The values obtained for all the formulations are given in the table. The thickness was approximately close to every formulation. It depends on polymer ratio. The folding endurance was measured in triplicate, according to procedure and the folding endurance was found to be 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. The formulation F3 showed lowest moisture content than other formulation. This is due to polymer ratio (like Ethyl cellulose). Lower moisture content in transdermal patch is good to prevent the brittleness with 100% dryness and it also maintains the stability of formulation. If formulation content has higher moisture content then it can lead to microbial contamination during the storage of patchs. The moisture uptake of F3 formulation was also low which could protect the formulation from microbial contamination reduce bulkiness. 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 %. The picture of patch (F1 formulation) was clear and also show the drug was uniformly distributed in it was an optimized formulation The *in-vitro* permeation study was done to see the effect of polymers through the Franz diffusion cell from patch having HPMC, EC in different conc. to optimized formulation for *in-vitro* study.

All the formulation was studied and all data fitted on zero order and first order, to explain the diffusion mechanism and pattern.

The % cumulative drug release was calculated over the study time range in 0-10 h. 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 F3 was to be found higher as compared to other formulation.

Stability studies were carried out with optimized formulation which was stored for a period of one, two and three months at 40±2 °C temperature and 75±5% relative humidity for a period 3 months. The % assay of formulation was determined by U.V. spectrophotometer using calibration curve method. The % assay of tablets was found to slightly decrease at higher temperature. Minor difference was found between evaluated parameters before and after ageing/storage and all was in acceptable limits. Therefore formulation remains stable for sufficient time.

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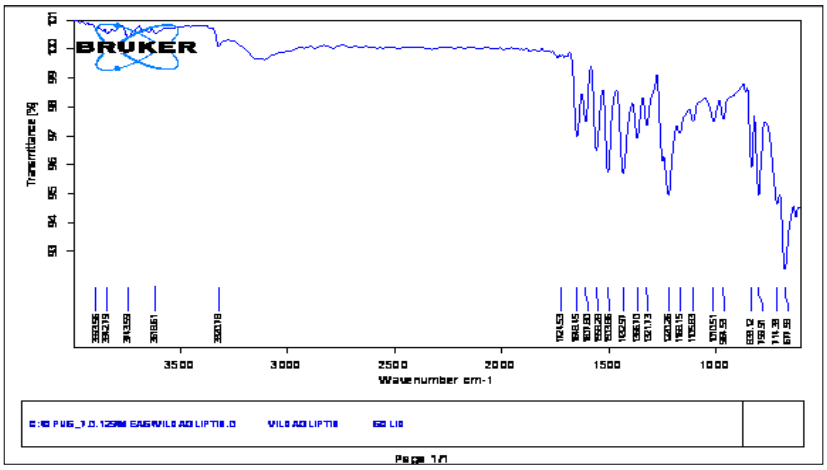

Figure 4: IR spectra of standard vildagliptin

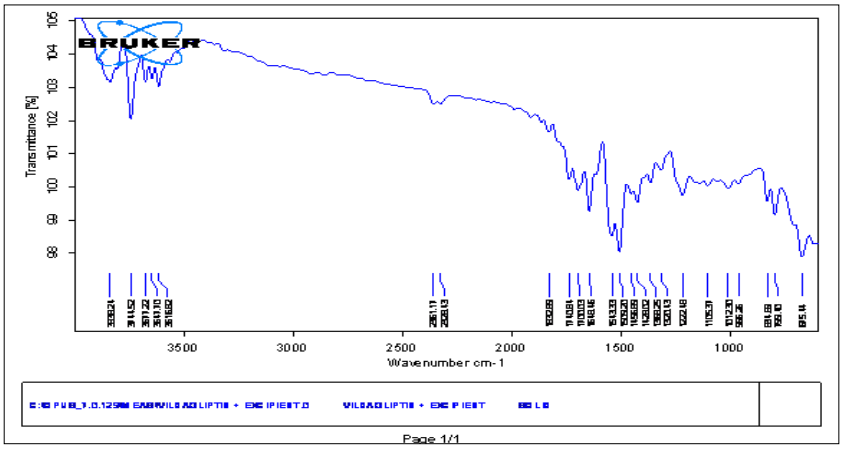

Figure 5: IR spectra of standard vildagliptin + excipient

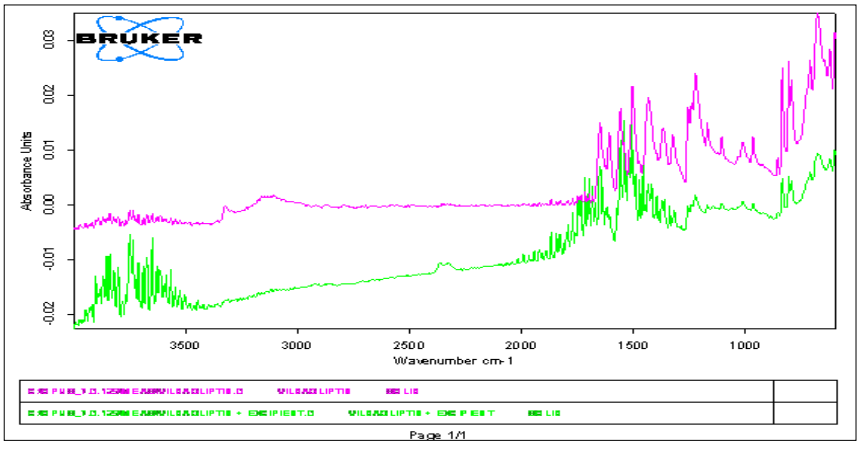

Figure 6: IR overlain spectra of standard vildagliptin & vildagliptin+excipient

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Table 11: Thicknesses and folding endurance of different formulations

S. No.	Formulation code	Thickness (mm)*	Folding endurance*
1.	F1	78±2	MT 250±2
2.	F2	83±3	MT 250±3
3.	F3	85±5	MT 250±5
4.	F4	87±3	MT 250±6
5.	F5	88±7	MT 250±3
6.	F6	92±8	MT 250±3

*(n=3±SD)

Table 12: % Moisture content and moisture uptake of different formulations

S. No.	Formulation code	% Moisture content	% Moisture uptake
1.	F1	4.2±0.4	5.2±0.25
2.	F2	4.5±0.3	5.8±0.47
3.	F3	3.9±0.5	6.9±0.65
4.	F4	4.9±0.7	4.5±0.58
5.	F5	5.1±0.5	4.9±0.74
6.	F6	5.2±0.4	4.2±0.45

*(n=3±SD)

Table 13: Percentage drug content of all the formulations

S. No	Formulation Code	% Drug Content
1	F1	91.25±0.45
2	F2	88.45±0.36
3	F3	98.56±0.45
4	F4	92.12±0.35
5	F5	93.45±0.65
6	F6	95.65±0.45

*(n=3±SD)

.

Table 14: *In vitro* % permeation profile of vildagliptin in formulation F1-F6

Time	% of Drug release					
(hr)	F1	F2	F3	F4	F5	F6
0.5	33.65	29.98	25.45	20.25	18.56	12.25
1.0	45.65	43.25	40.25	35.56	30.25	25.65
2.0	59.98	50.56	48.98	40.12	35.65	33.25
4.0	69.98	63.32	60.25	50.56	42.15	45.65
6.0	98.78	90.12	85.65	55.45	52.23	51.12
8.0	99.12	98.89	95.45	65.65	61.14	62.25
10.0	99.45	98.95	98.98	81.21	65.45	66.45

Table 15: Kinetic data of vildagliptin transdermal patches

Formulation code	Regression coefficient	
	Zero order	First order
F3	0.948	0.937

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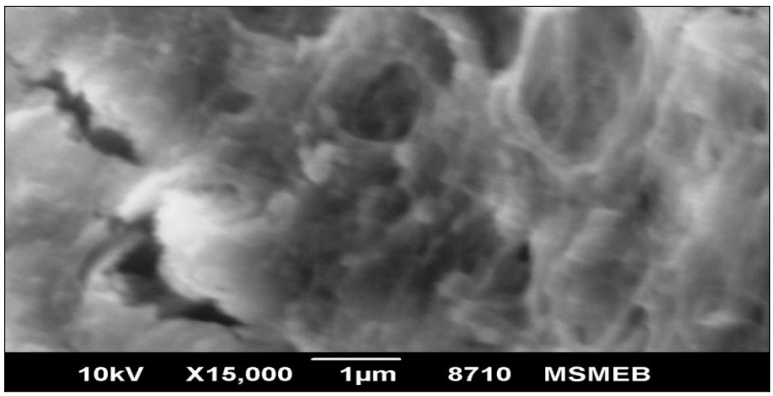

Figure 7: SEM Image of F-1 formulation

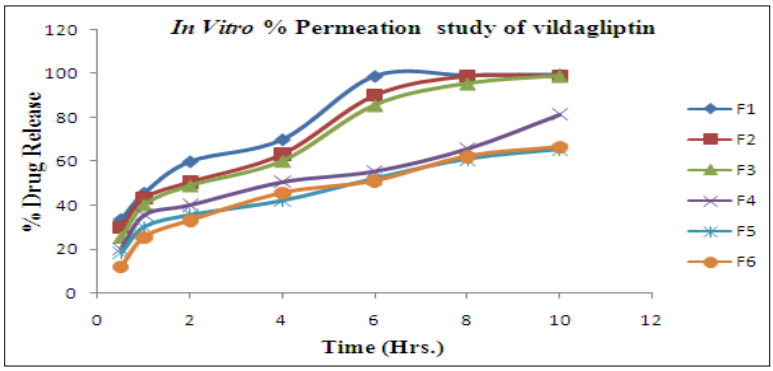

Figure 8: *In vitro* % permeation profile of vildagliptin in formulation F1-F6

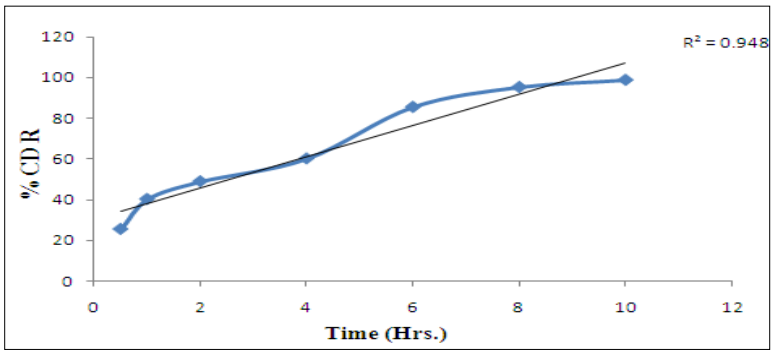

Figure 9: Zero order release kinetic profile of formulation F3

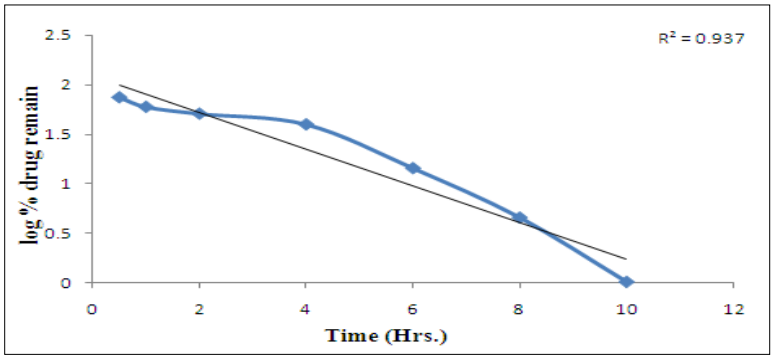

Figure 10: Zero order release kinetic profile of formulation F3

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Conclusion

The transdermal patches of vildagliptin were prepared using the combination of polymers in different concentration with permeation enhancer and plasticizer was found to be completely compatible with the drug molecule and the designed formulation release the drug in a sustained fashion over a prolonged period of time. The formulation F3 showed a maximum release and permeation of drug for a longer time period up to 12 h. Hence, it can be concluded that vildagliptin can be successfully formulated as the transdermal patch that can release the drug for an extended period of time up to 12 hours in a sustained manner. Such a drug delivery system can be used to avoid the side effects associated with the therapy and can safely deliver the drug with better patient compliance.

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