FORMULATION AND CHARACTERIZATION OF VILDAGLIPTIN LOADED TRANSFEROSOMAL GEL FOR TRANSDERMAL DELIVERY

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Abstract: -

The age-old theory that imparted the status of "dead impermeable barrier devoid of biological activity" to skin had already been challenged by the development of pioneering transdermal gel. TDDS in the year 1980 by Alza Corporation of USA and subsequently introduction of many other drugs by other companies such as nitroglycerin, fentanyl, clonidine, vildagliptin etc. The extensive work in the last 25 years both by academicians and industrialists in the area of transdermal delivery have generated more than ten marketed products. But this route of administration continues to be limited owing to the scarcity of suitable drug candidates available. To focus these developments and the important criteria for the selection of drug, the objectives and plan of work have been discussed. The results indicated that, there was reduction in folding endurance values in 6 months, this change may be due loss of moisture. However, the rate of degradation of drug was not significant indicating that the drug is stable further, the integrity of the permeation enhancer was assessed by *ex vivo* permeation at regular time intervals during the accelerated stability studies. The permeation rate did not alter significantly up to 6 months. These results were found to agree well with the DSC spectral data and SEM results.

Keywords: TDDS, DSC, vildagliptin, SEM, etc.

INTRODUCTION

The potential of utilizing intact skin as a means of drug administration has been acknowledged for several decades, as exemplified by the development of medicated patches in countries like China and Japan. This practice likely ignited curiosity in exploring the skin as a pathway for delivering drugs to produce systemic effects. The discovery of this delivery route represents a

significant advancement in the field of controlled drug delivery systems. The transdermal drug delivery system (TDDS) stands out for its ability to transport drugs through intact skin, thereby bypassing the initial metabolism in the body. This has driven an upsurge in research efforts in the realm of transdermal drug delivery[1,2].

SKIN - SITE FOR TRANSDERMAL ADMINISTRATION:

The adult human skin covers an approximate area of 2 square meters and has an average thickness of about 2.5 millimeters. Its density is approximately 1.1 grams per cubic centimeter, and it constitutes roughly 6% of the total body weight. Human skin serves a dual purpose. On one hand, it acts as a protective barrier, shielding the body from chemical, physical, and microbial threats, preventing the loss of water and other endogenous substances. On the other hand, it plays a crucial role in regulating the body's temperature and functions as an excretory organ.[3]

This multifunctional capability of the skin is attributed to its highly specialized structure, with the primary barrier function situated in the outermost layer known as the stratum corneum.[4-5]

FACTORS CONTROLLING TRANSDERMAL PERMEABILITY[1]:

The factors controlling transdermal permeability can be broadly classified as:
Physico-chemical properties of the penetrant molecules:
1. Partition coefficient: Drugs that exhibit solubility in both lipid and water are more likely to be effectively absorbed through the skin. The transdermal permeability coefficient demonstrates a proportional relationship with the partition coefficient. Typically, a partition coefficient of one or greater, favoring the lipid phase, is generally necessary for optimal transdermal absorption.
2. pH conditions: Skin can be adversely affected by extremely high or very low pH levels. When the pH is within a reasonable range, however, the flux of ionizable medicines may be influenced due to pH-induced alterations that alter the balance between charged and uncharged species, affecting their transdermal permeability.
3. Penetrant concentration: The flow of the medication via the skin increases as the concentration of dissolved drug increases. At greater concentrations, any surplus solid drug acts as a reservoir, assisting in maintaining a steady drug concentration over time.

PHYSICO-CHEMICAL PROPERTIES OF DRUG DELIVERY SYSTEMS:
The physico-chemical properties of drug delivery systems play a pivotal role in determining their effectiveness and behavior in delivering medications. Several key properties deserve attention:
1. Solubility: The solubility of the drug within the delivery system is essential. It influences the drug's release rate, as highly soluble drugs may diffuse more rapidly.
2. Particle Size: The size of drug particles within the delivery system can significantly affect their release. Smaller particles often lead to faster dissolution and release.
3. Chemical Stability: The stability of both the drug and the components of the delivery system is crucial. Chemical reactions within the system can alter drug release rates and effectiveness.

4. Mechanical Properties: The mechanical strength and properties of the delivery system, including its viscosity and elasticity, influence its ability to adhere to the skin or mucosal surfaces.

5. Hydrophobicity/Hydrophilicity: The affinity of the delivery system for water can impact drug release. Hydrophobic systems may release drugs more slowly than hydrophilic ones.

ANATOMY OF TRANSDERMAL DRUG DELIVERY SYSTEMS:
Additives:

1. Release liner: The release liner is a critical component of transdermal drug delivery systems, serving as the protective barrier that covers the adhesive side of the patch. This liner is typically made of a non-stick material, such as silicone-coated paper or plastic. The design and properties of the release liner are carefully chosen to ensure efficient and safe application of the drug delivery system while maintaining the patch's integrity and sterility.[6].

2. Backing layer: The backing layer is a vital component within transdermal drug delivery systems, positioned on the side opposite to the drug-containing adhesive matrix. It is typically constructed from a thin, flexible, and impermeable material like polyester or aluminum. Additionally, the backing layer contributes to the patch's overall durability, flexibility, and ease of handling. Its impermeability also directs drug delivery in one direction, ensuring controlled release through the skin while preventing backflow.[7-8].

3. Adhesive layer: [8] A change in lipid composition occurs as these keratinocytes get closer to the skin's surface. While the sphingolipid and cholesterol level eventually rises, the phospholipid content gradually decreases. The differentiation process, which occurs when the cells advance to the epidermis' outermost layers, includes a shift in lipid composition.

4. "Convenience of use (PSAs do not require water/solvents or heat in order to achieve adhesion)
➢ Good stability (PSAs are generally not sensitive to environmental humidity or temperature degradation)
➢ Simplicity of manufacture
➢ Good appearance"[9,10].

5. Overlay: This additional element is designed to be applied over an already positioned transdermal patch that is adhered to the patient's skin. The primary function of this overlay is to secure the medicated patch firmly in place on the patient's skin, ensuring that it remains in position during use. It enhances the adhesion and stability of the transdermal patch, helping to prevent unintentional detachment or displacement.

6. Membrane: The primary role of the membrane is to govern the release of the drug and any

excipients to the skin by controlling their diffusion properties. This regulation is critical for achieving the intended rate and extent of drug delivery through the skin. The membrane's selective permeability ensures a controlled and consistent release of the drug, allowing for precise dosing and therapeutic efficacy in transdermal drug delivery systems.

MATERIALS AND METHODS
The materials that were either AR/LR grade or the best possible Pharmaceutical grade available were used as supplied by the manufacturer.

Procedure for the preparation of Transferosomal gel:
The polymers in selected ratios as represented in Table 9-14 were weighed and dissolved in specified solvent system. The plasticizer was added to the polymeric solution and mixed uniformly. Finally the drug was incorporated with continuous agitation and the volume was made up to 10ml. The films were prepared by casting the drug loaded polymeric solutions in an flat bottemed petridish. The casting solution was dried at room temperature for a period of 24h. and stored in desiccators until further studies.

RESULTS AND DISCUSSION
UV Estimation of vildagliptin:

Figure 1: UV spectrum of vildagliptin in pH 7.4 phosphate buffer
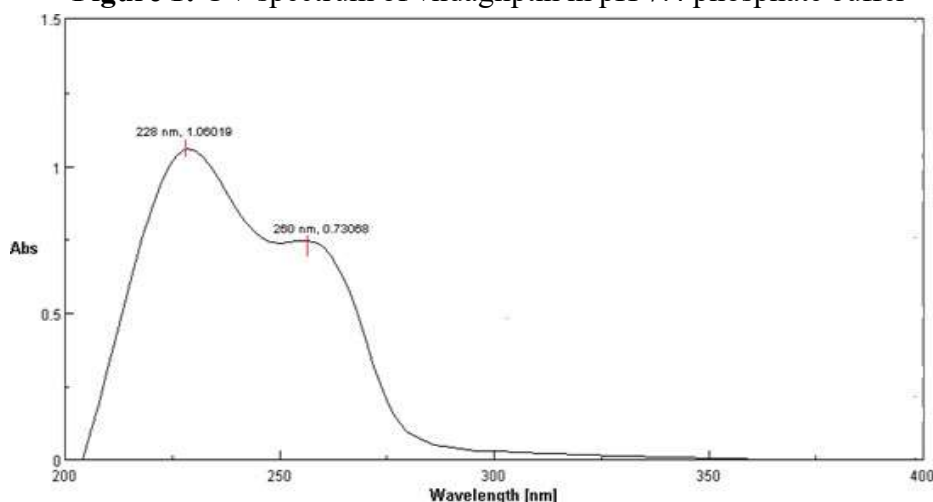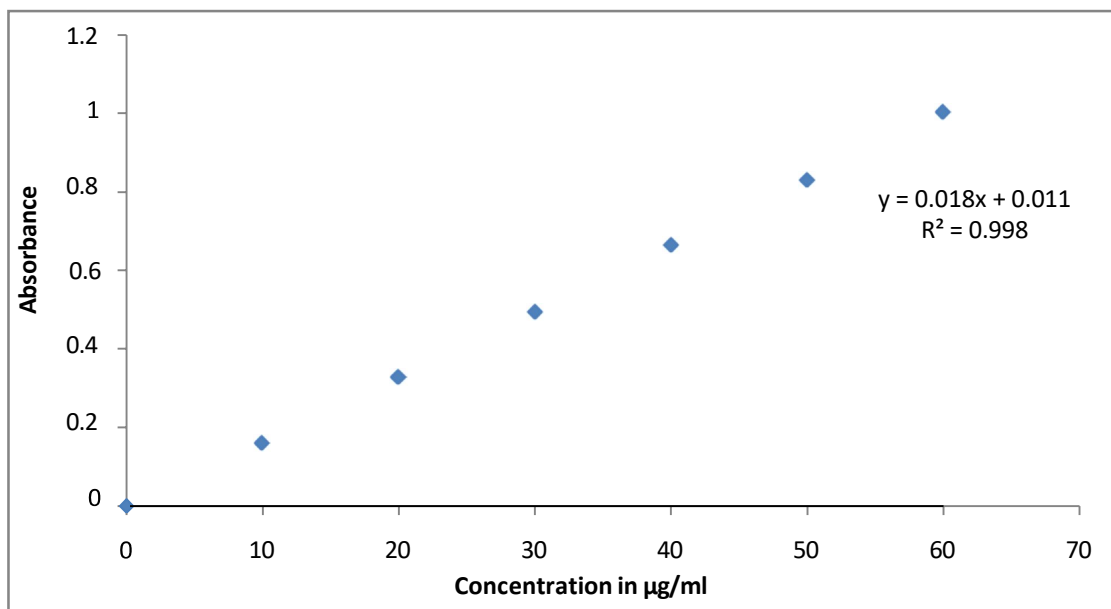

The UV spectrum of vildagliptin in phosphate buffer pH 7.4 showed λ_{max} at 260 nm. The spectrum displaying the absorption maxima and calibration curve are shown in Figure 1 and Graph 1 respectively.

Table 1: Data for standard curve of vildagliptin in phosphate buffer 7.4 pH at 260 nm

Sl. No.	Volume of SS-II (ml)	Volume made up to (ml)	Conc. (µg/ml)	Absorbance at 260 nm				
				Trail 1	Trail 2	Trail 3	Average	± S.D.
1	0.5	10	10	0.159	0.161	0.163	0.161	±0.001

2	1.0	10	20	0.332	0.326	0.329	0.329	±0.001
3	1.5	10	30	0.491	0.496	0.499	0.495	±0.001
4	2.0	10	40	0.662	0.663	0.669	0.665	±0.000
5	2.5	10	50	0.828	0.830	0.834	0.831	±0.001
6	3.0	10	60	1.005	1.004	1.001	1.003	±0.001

y = 0.018x + 0.011
R² = 0.998

Graph 2: Standard Calibration Curve of vildagliptin in phosphate buffer 7.4 pH

The linear regression analysis for standard curve:

Linear regression analysis was done on Absorbance data points:

The slope   =   0.018
The intercept   =   0.011
The correlation coefficient   =   0.998

A straight line equation (**Y = mx + c**) was generated to facilitate the calculation.

Absorbance = 0.018 × Concentration + 0.011

The absorbance values and the calibration curve are shown in Table 1 and Graph 1.
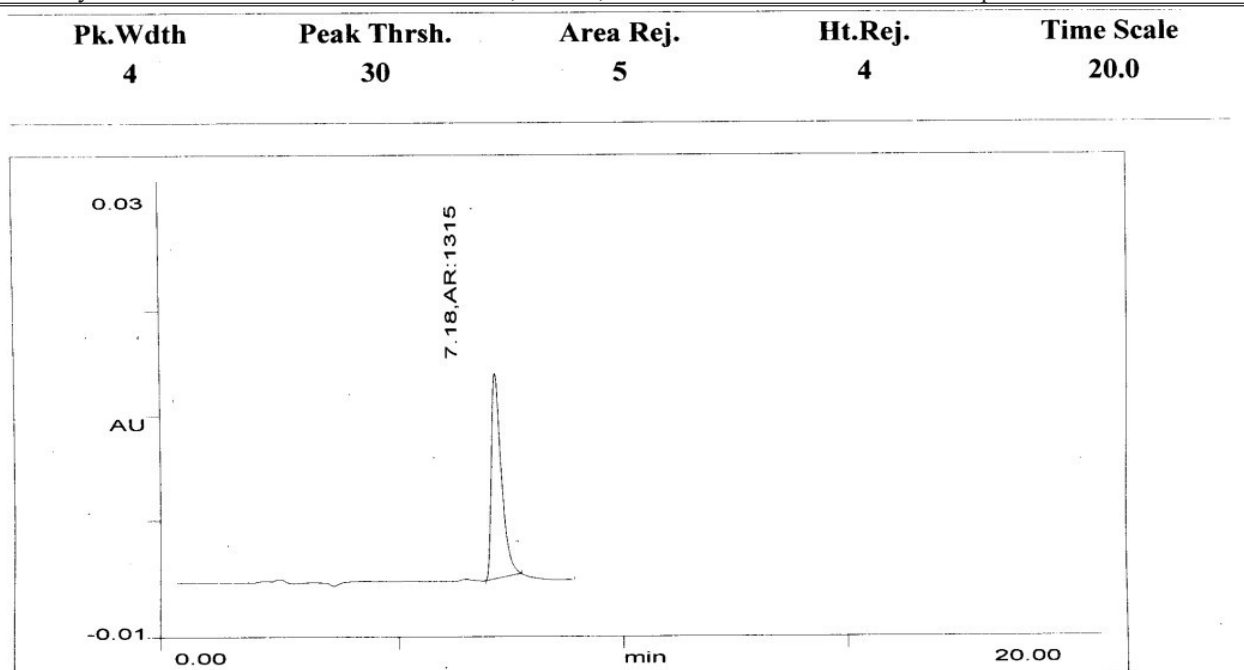
Estimation of vildagliptin by HPLC method:

Pk.Wdth	Peak Thrsh.	Area Rej.	Ht.Rej.	Time Scale
4	30	5	4	20.0

Figure 2: HPLC Chromatogram of vildagliptin Table .

## EVALUATION OF VILDAGLIPTIN TRANSFEROSOMAL GEL:
Physicochemical charecteristics:
i. Gross visual appearance:

vildagliptin Transferosomal gel was visually inspected for clarity, flexibility and smoothness. Gel which was transparent, clear, smooth and flexible from each series were optimized for further investigation.

**ii. Surface morphology by scanning electron microscopy (SEM):**
It was observed from the SEM photographs that, the films exhibited uniform distribution of drug in all the polymeric matrices used. The SEM of vildagliptin Transferosomal gel films of HPMC 6cps, Eudragit RL & RS 100, PVP - Eudragit RS 100, PVP - EC, HPMC 6cps - EC and HPMC 6cps - PVP are shown in Figure2 & 3. Surface morphology of vildagliptin Transferosomal gel loaded HPMC 6 cps
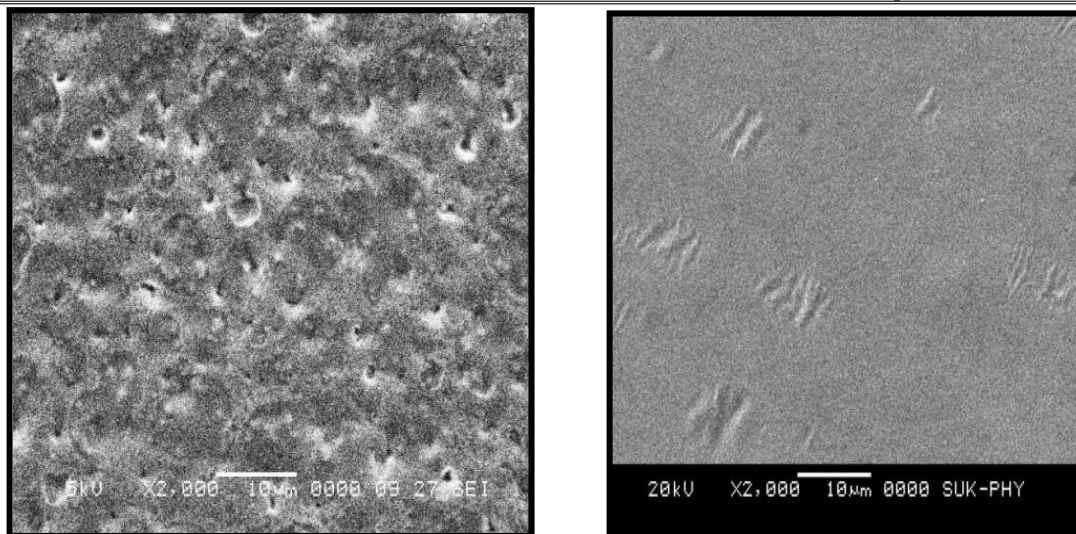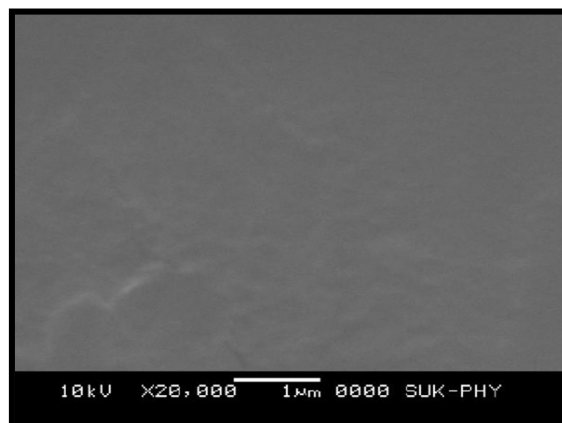
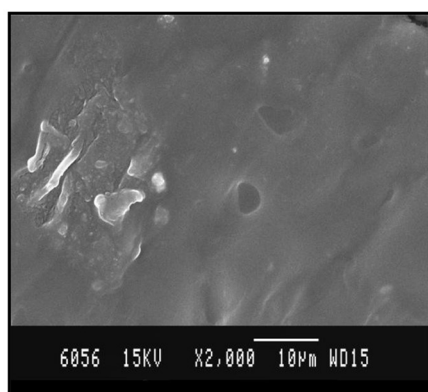A   B

Figure 3: SEM Photograph of vildagliptin containing TDDS of:
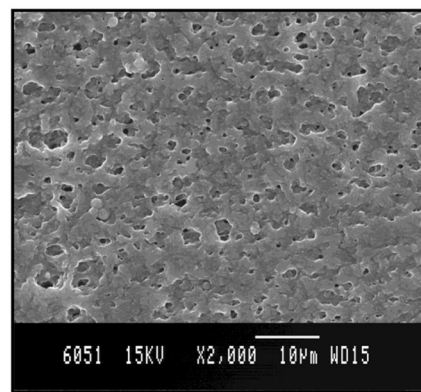A) HPMC 6cps, B) Eudragit RL-RS 100
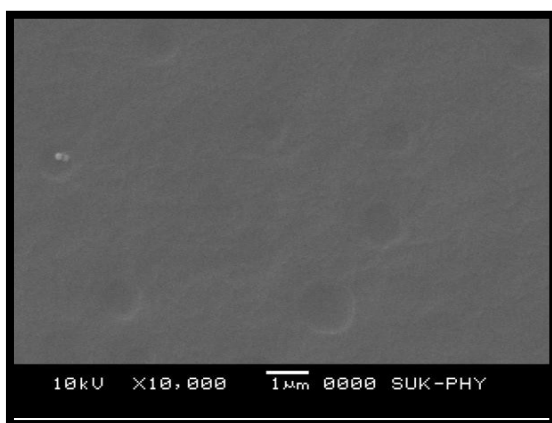
C   D

E   F

Figure 4: SEM Photograph of vildagliptin containing TDDS of:C) PVP-Eudragit,

D) PVP-EC, E) HPMC-EC and F) HPMC 6cps-PVPand HPMC-PVP gel were pitted and surface characters were not smooth. PVP- Eudragit RS 100 and PVP-EC gel were smooth and also there was no evidence of drug in crystalline form. However crystalline drug was evident in case of HPMC-EC patches. Based on these observations it is evident that, PVP-Eudragit and PVP-EC gel were able to produce gel with smooth finish and drug is in amorphous state and distributed uniformly.

iii. Thickness of the gel:

Thickness of the vildagliptin gel of different series were found to be ranging from 0.037 to 0.22 mm (± SD n=3), HPMC gel was thin and HPMC-PVP gel were thicker as compared to gel of other series.

iv. Weight uniformity:

Weight of the gel ranged from 0.430 to 2.010 gm, HPMC gel were lighter, while HPMC-EC gel were heavier as compared to other series. Standard deviation values indicated that, weights were uniform.

Sl. No.	Formulation code	Thickness of the gel in mm	Weight uniformity in g	Percentage drug content
1	NHPM-1	0.037 ±0.42	0.43 ±0. 94	96.53 ±2.57
2	NHPM-2	0.042 ±0.54	0.44 ±0.54	96.92 ±1.58
3	NHPM-3	0.074 ±0.81	0.43 ±0.88	97.71 ±3.06
4	NELS-1	0.14 ±0.75	0.84 ±1.24	98.10 ±2.10
5	NELS-2	0.13 ± 0.56	0.87 ±1.00	97.32 ±1.88
6	NELS-3	0.12 ±0.84	0.90 ±1.34	95.74 ±2.22
7	NELS-4	0.12 ±1.21	0.86 ±1.40	94.95 ±3.10
8	NELS-5	0.13 ±1.00	0.92 ±1.22	94.16 ±2.06
9	NELS-6	0.11 ± 0.98	0.87 ±1.10	92.19 ±1.84
10	NELS-7	0.11 ±1.22	0.82 ±0.82	91.01 ±1.62
11	NELS-8	0.13 ±1.34	0.85 ±0.98	97.32 ±1.72

Table 3: Physicochemical properties of vildagliptin containing HPMC & Eudragit RL-RS 100 gel

Table 4: Physicochemical properties of vildagliptin containing PVP-Eudragit RS 100 & PVP-EC patches

Sl. No.	Formulation code	Thickness of the films in mm	Weight uniformity in g	Percentage drug content
1	NRPS-1	0.14 ±0.58	1.01 ±1.00	93.34 ±2.88
2	NRPS-2	0.15 ±0.88	0.98 ±1.84	94.22 ±0.88
3	NRPS-3	0.13 ±0.42	0.88 ±1.24	90.18 ±2.06
4	NRPS-4	0.15 ±0.94	0.96 ±1.12	92.15 ±2.57
5	NRPS-5	0.12 ±0.64	0.84 ±1.40	92.91 ±2.23
6	NRPS-6	0.12 ±0.88	0.87 ±1.00	95.99 ±1.58

7	NRPS-7	0.10 ±0.56	0.96 ±1.48	90.42 ±1.56
8	NRPS-8	0.12 ±0.78	0.97 ±1.24	90.58 ±1.57
9	NRPS-9	0.15 ±0.74	0.87 ±1.10	92.28 ±1.22
10	NPEC-1	0.14 ±0.98	1.10 ±1.46	95.19 ±2.06
11	NPEC-2	0.17 ±0.78	1.18 ±1.20	90.33 ±1.57
12	NPEC-3	0.14 ±0.88	1.247 ±1.42	91.58 ±1.72
13	NPEC-4	0.13 ±0.01	1.11 ±0.98	92.42 ±1.78

Table 5: Physicochemical properties of vildagliptin containing HPMC-EC & HPMC-PVP patches

| Sl. No.	Formulation code	Thickness of the films in mm	Weight uniformity in g	Percentage drug content
1	NHEC-1	0.10 ±0.52	0.75 ±1.20	96.53 ±2.24
2	NHEC-2	0.12 ±0.88	0.63 ±1.88	96.92 ±0.90
3	NHEC-3	0.12 ±0.66	0.67 ±1.32	97.71 ±2.02
4	NHEC-4	0.13 ±0.90	0.64 ±1.33	92.15 ±2.20
5	NHEC-5	0.12 ±0.78	0.71 ±1.45	97.66 ±2.46
6	NHEC-6	0.13 ±0.92	0.72 ±1.00	98.10 ±1.54
7	NHPV-1	0.21 ±0.64	1.99 ±1.46	96.66 ±1.58
8	NHPV-2	0.20 ±0.78	2.01 ±1.28	97.60 ±1.48
9	NHPV-3	0.19 ±0.79	1.96 ±1.40	98.56 ±1.26
10	NHPV-4	0.22 ±0.98	1.98 ±1.44	98.10 ±2.76
11	NHPV-5	0.21 ±0.68	1.89 ±1.24	98.50 ±1.57
12	NHPV-6	0.20 ±0.80	2.00 ±1.46	98.89 ±1.98

v. Percentage drug content:

Drug content values for all the formulated gel ranged from 90 to 98% of the theoretical content with minimum standard deviation values (n=3) which indicates that, drug is uniformly distributed in the polymer, hence the method employed was capable of giving uniform drug content with minimum batch variability. Values for the various physico-chemical parameters are shown in Table 3-4.
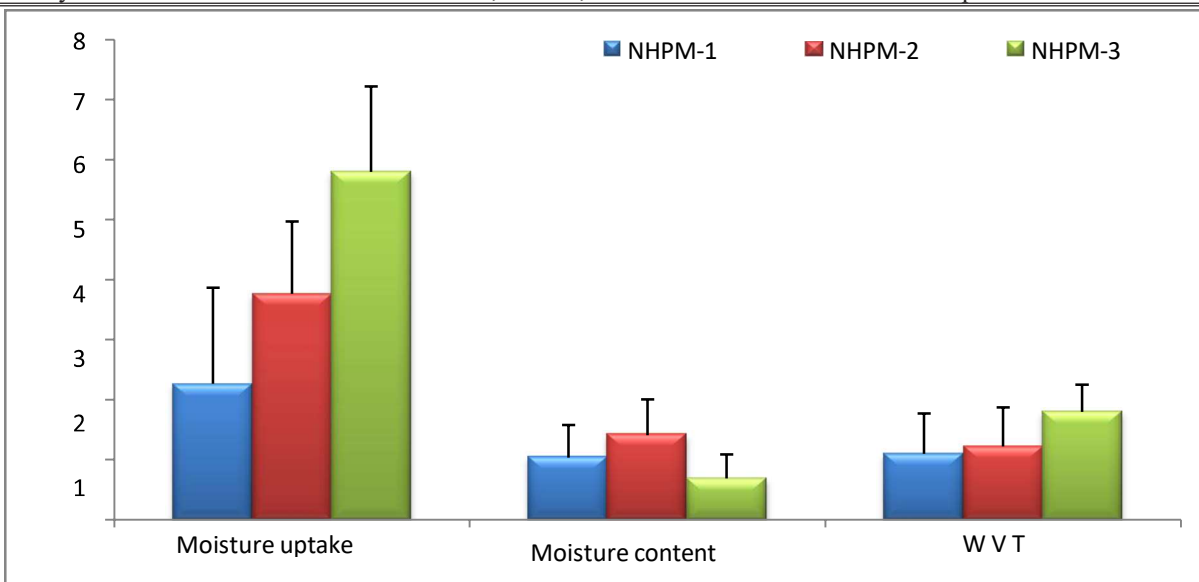
vi. Percentage moisture uptake:

Physicochemical studies like moisture uptake and moisture content provides information regarding the stability of the formulation[112]. Moisture uptake capacity of gel made from different combination of polymers ranged from as low as 1.71 to as high as 14.17 %. HPMC, Eudragit RL-RS 100 and HPMC-EC combination gel showed minimum water uptake capacity as compared to PVP-Eudragit RS 100, PVP- EC and HPMC-PVP gel. Among these, PVP-Eudragit RS 100 combination exhibited highest moisture uptake capacity.

Table 5: Physicochemical properties of vildagliptin loaded HPMC & Eudragit RL-RS 100 gel

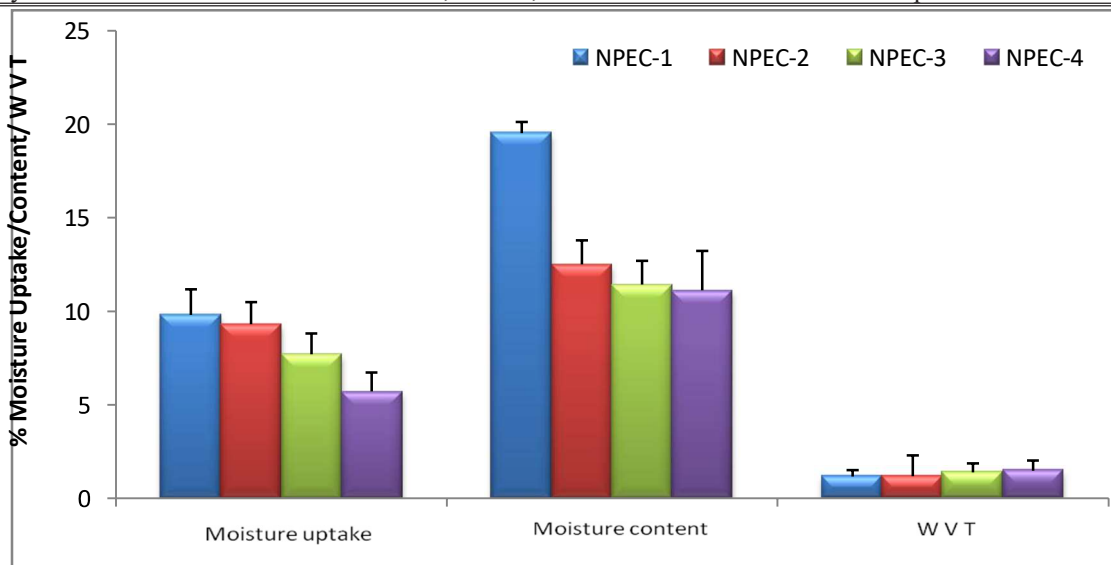| SL. No.	Formulation code	Percentage moisture uptake	Percentage moisture content	Water vapor transmission(WVT) in (gm.cm/cm^2.24h)
			$\pm$ SD (n=3)	
1	NHPM-1	2.27 $\pm$1.60	1.04 $\pm$0.54	1.10 $\times$ 10^{-3} $\pm$0.67
2	NHPM-2	3.77 $\pm$1.20	1.41 $\pm$0.60	1.22 $\times$ 10^{-3} $\pm$0.65
3	NHPM-3	5.80 $\pm$1.42	0.69 $\pm$0.40	1.80 $\times$ 10^{-3} $\pm$0.45
4	NELS-1	3.15 $\pm$0.24	7.46 $\pm$0.54	5.77 $\times$ 10^{-4} $\pm$0.36
5	NELS-2	2.89 $\pm$0.12	6.98 $\pm$0.86	4.77 $\times$ 10^{-4} $\pm$0.62
6	NELS-3	2.87 $\pm$0.36	6.08 $\pm$0.48	4.19 $\times$ 10^{-4} $\pm$0.45
7	NELS-4	2.65 $\pm$0.10	6.00 $\pm$0.65	3.89 $\times$ 10^{-4} $\pm$0.10
8	NELS-5	2.38 $\pm$0.12	5.27 $\pm$1.08	3.65 $\times$ 10^{-4} $\pm$0.86
9	NELS-6	2.19 $\pm$0.80	3.98 $\pm$0.20	3.26 $\times$ 10^{-4} $\pm$0.95
10	NELS-7	1.71 $\pm$0.45	3.93 $\pm$0.40	2.85 $\times$ 10^{-4} $\pm$0.88
11	NELS-8	3.11 $\pm$0.63	6.97 $\pm$0.70	5.02 $\times$ 10^{-4} $\pm$0.22
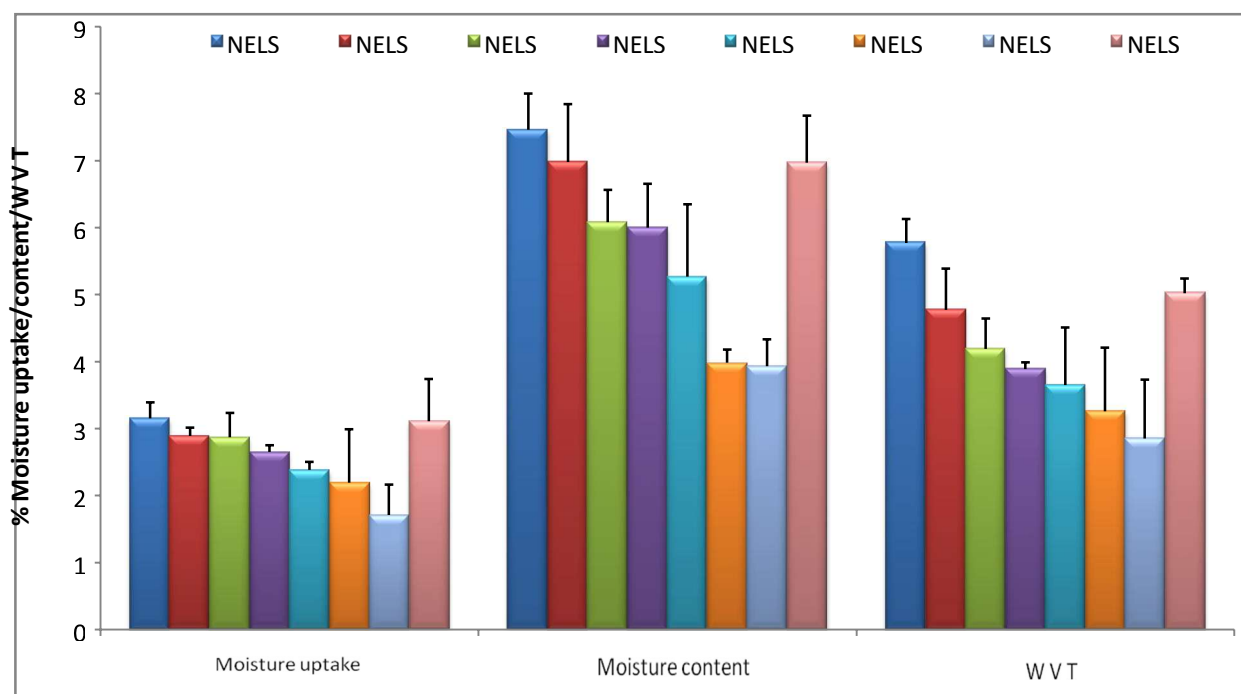
Graph 6: Percentage moisture uptake, moisture content and W V T of drug loaded HPMC gel
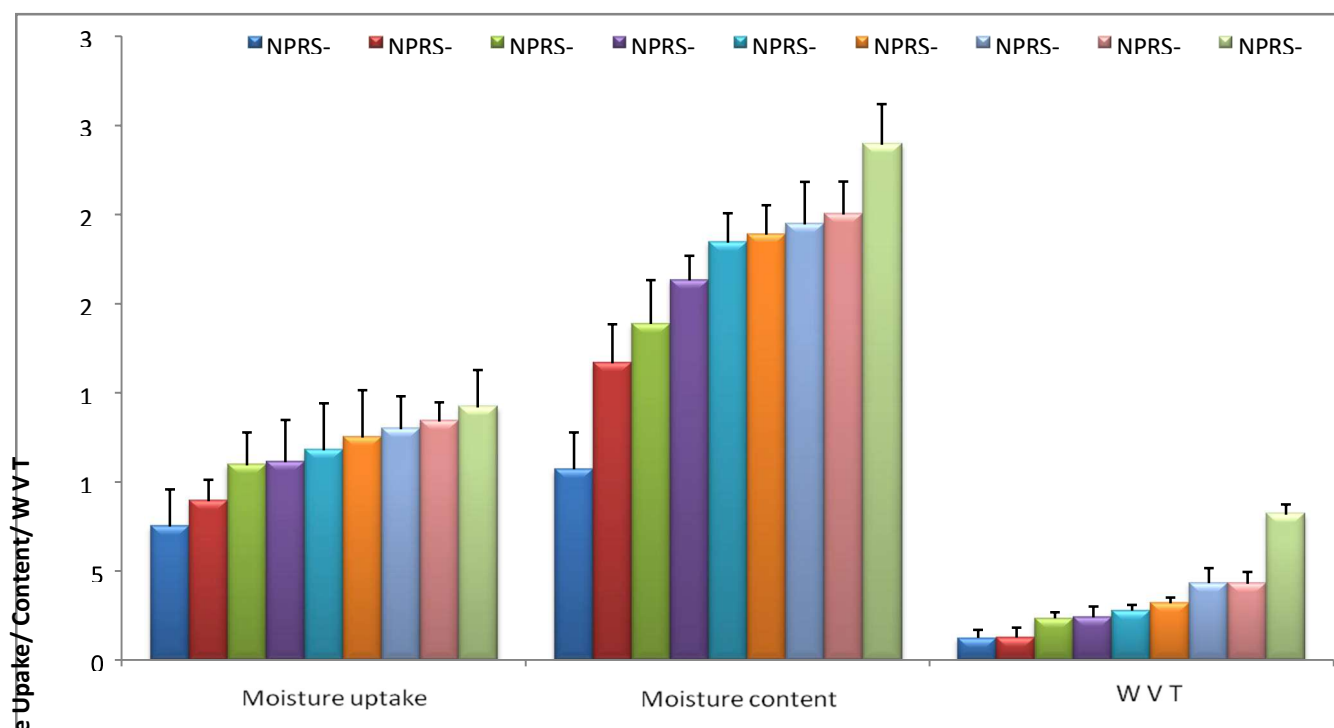
Graph 7: Percentage moisture uptake, moisture content and W V T of drug loaded Eudragit RL-RS 100 gel

Table 6: Physicochemical properties of vildagliptin loaded PVP-Eudragit RS 100 & PVP-EC gel

| SL. No.	Formulation code	Percentage moisture uptake	Percentage moisture content	Water vapor transmission (WVT) in (gm.cm/cm^2.24h)
± SD (n=3)				
1	NPRS-1	7.50 ±0.88	10.71±2.06	1.24×10^{-3}±0.45
2	NPRS-2	8.92 ±0.70	16.66 ±2.18	1.27×10^{-3} ±0.55
3	NPRS-3	10.93 ±1.84	18.86 ±2.46	2.34×10^{-3} ±0.35
4	NPRS-4	11.11 ±2.36	21.31 ±1.38	2.40×10^{-3} ±0.60
5	NPRS-5	11.76 ±2.65	23.43 ±1.65	2.77×10^{-3}±0.32
6	NPRS-6	12.50 ±1.64	23.88 ±1.62	3.19×10^{-3} ±0.75
7	NPRS-7	12.96 ±1.84	24.46 ±2.38	4.32×10^{-3} ±0.84
8	NPRS-8	13.39 ±1.08	25.00 ±1.86	4.29×10^{-3} ±0.66
9	NPRS-9	14.17±2.10	28.92 ±2.28	8.17×10^{-3} ±0.57
10	NPEC-1	9.80 ±2.36	19.51 ±1.60	1.16×10^{-3} ±0.35
11	NPEC-2	9.30 ±2.28	12.50 ±2.10	1.18×10^{-3}±0.75
12	NPEC-3	7.69 ±2.12	11.42±2.26	1.38×10^{-3} ±0.47
13	NPEC-4	5.71 ±1.96	11.11 ±2.10	1.47×10^{-4} ±0.54

Graph 8: Percentage moisture uptake, moisture content and WVT of drug loaded PVP-EC gel

Graph 9: Percentage moisture uptake, moisture content and W V T of drug loaded PVP-Eudragit RS 100 g e l

Table 7: Physicochemical properties of vildagliptin loaded HPMC-EC & HPMC-PVP gel

SL. No.	Formulation code	Percentage moisture uptake	Percentage moisture content	Water vapor transmission (WVT) in (gm.cm/cm^2.24h)	
± SD (n=3)					
1	NHEC-1	2.98 ±0.65	10.45 ±1.68	5.86 × 10^{-4} ±0.42	
2	NHEC-2	3.48 ±0.23	12.23 ±1.24	7.53 × 10^{-4} ±0.65	
3	NHEC-3	4.31 ±0.34	15.77 ±1.30	7.97 × 10^{-4} ±0.84	
4	NHEC-4	4.45 ±0.68	16.00 ±1.28	8.46 × 10^{-4} ±0.90	
5	NHEC-5	5.22±0.82	19.77 ±1.00	9.46 × 10^{-4} ±0.82	
6	NHEC-6	4.72±0.66	15.94 ±1.34	8.63 × 10^{-4} ±0.68	
7	NHPV-1	6.23 ±0.34	3.15 ±0.84	8.90 × 10^{-4} ±0.44	**60**
8	NHPV-2	7.64 ±0.68	3.88 ±0.32	9.98 × 10^{-4} ±0.64	
9	NHPV-3	8.73 ±0.44	4.21 ±0.38	8.12 × 10^{-4} ±0.54	
10	NHPV-4	5.75 ±0.48	2.86 ±0.40	7.85 × 10^{-4} ±0.40	
11	NHPV-5	5.17 ±0.82	2.15 ±0.30	8.85 × 10^{-4}±1.02	
12	NHPV-6	9.04 ±0.94	4.87 ±0.60	8.82 × 10^{-4} ±0.65	
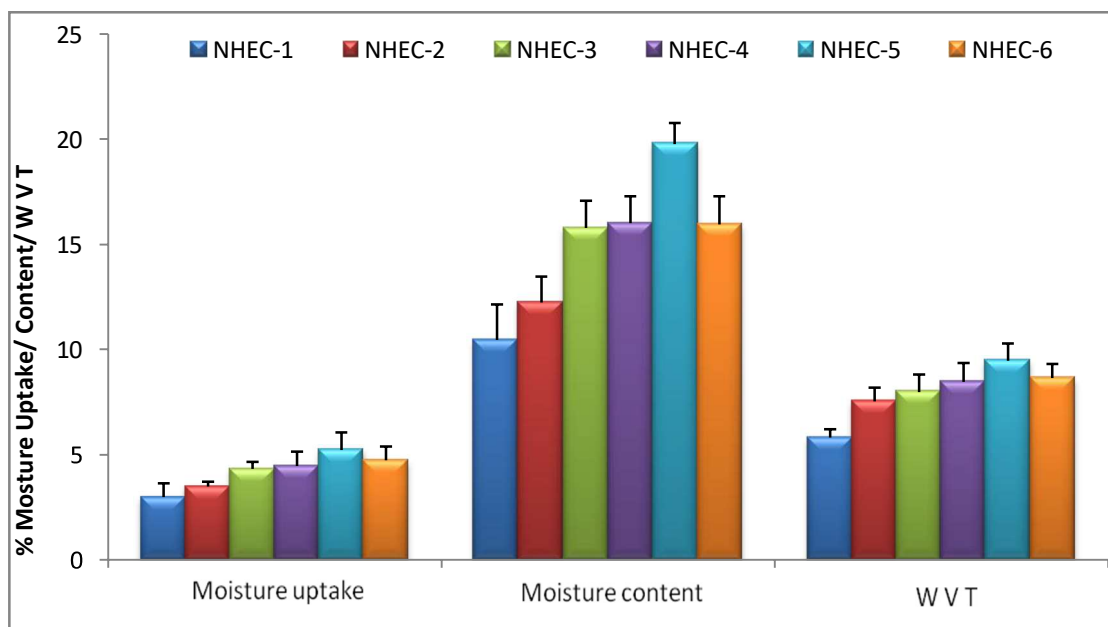
Graph 10: Percentage moisture uptake, moisture content and WVT of drug loaded HPMC-EC gel

SUMMARY AND CONCLUSION

Transdermal systems prove to be highly suitable for the management of chronic diseases that necessitate ongoing treatment. Diabetes, which affects a substantial portion of the population, is one such condition that requires continuous care. Additionally, it is worth noting that cancer ranks as the disease with the highest mortality rate. Patients suffering from various medical conditions,

including diabetes, often require regular monitoring of vital parameters like blood pressure. This monitoring necessitates frequent drug administration, typically through traditional oral routes, to ensure effective disease management. In such cases, transdermal drug delivery systems offer a promising alternative, potentially enhancing the convenience and efficacy of treatment. In this context transdermal drug delivery has proved to be a viable alternative for the delivery of drugs to systemic circulation. Hence, matrix type of Transferosomal gel of vildagliptin has proved to be promising and warrants further clinical evaluation in effective management of diabetes. Today, TDDS have proved to reduce diabetes significantly. Hence, from these results it could be inferred that, the aims and objectives of the present work were found to be satisfactory.

FUNDING

Nil.

CONFLICT OF INTEREST

None.

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