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FORMULATION AND EVALUATION OF TOPICAL DRUG DELIVERY FOR WOUND HEALING IN DIABETICS PATIENTS

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Abstract:

The main aim of our research was to development And Evaluation of Topical Drug Delivery for Wound Healing in Diabetic Patients. Topical route is most suitable route for skin infections. The development of topical drug delivery systems designed to have systemic effects appears to be beneficial for a number of drugs on account of the several advantages over conventional routes of drug administration. A novel cream formulation consisting of Vildagliptin was prepared. The formulation was subjected to in-vitro diffusion studies and in-vitro cell line study. No change of the physical properties was observed; the pH was in a proper range (approximately pH 4.60 to 5.78). The formulations showed good spread ability, no evidence of phase separation and good consistency during this study period. Prepared formulation show good drug release and in-vitro cell line study show the moderate wound healing activity. Batch F8 show the optimum drug release and good wound healing activity. So it is concluded that optimized batch is F8. From the present study it can be concluded that it is possible to develop creams containing Vildagliptin having wound healing property and can be used as the provision of a barrier to protect skin.

Keywords: Vildagliptin, cream, in-vitro cell line study, Spreadability.

Introduction:

Diabetes mellitus is globally prevalent, diabetic wound and ulcer is one of its most severe and expensive complications. Diabetic wound and ulcer results from an intricate interaction of a number of risk factors. Patients with diabetic wound and ulcers often require amputations of the lower limbs and, in more than half the cases, infection is the preeminent factor [1]. The healing of cutaneous wounds is a dynamic, complex, and well-organized process and requires the orchestration of many different cell types and cellular processes [2]. The classic model of wound healing is divided into three sequential phases: inflammation, proliferation, and maturation. Each phase is characterized by the sequential elaboration of distinctive cytokines by specific cells [3]. Adult skin consists of two major tissue layers: a keratinized stratified epidermis and an underlying thick layer of collagen-rich dermal connective tissue providing support and nourishment. Appendages such as hairs and glands are derived from, and linked to, the epidermis but project deep into the dermal layer. Because the skin serves as a protective barrier against the outside world, any break in it must be rapidly and efficiently mended. A temporary repair is achieved in the form of a clot that plugs the defect, and over subsequent days steps to regenerate the missing parts are initiated. Inflammatory cells and then fibroblasts and capillaries invade the clot to form a contractile granulation tissue that draws the wound margins together; meanwhile, the cut epidermal edges migrate forward to cover the denuded wound surface [4].

The objective of the present study was to develop formulations of Vildagliptin in different types of cream. The prepared creams were evaluated for physical appearance, pH, spreadability, viscosity, *in-vitro* drug release study and *in-vitro* cell line study.

Material and Method:

- **Material:**

Vildagliptin were provided by Ajanta Pharma Ltd, Mumbai as a gift sample Bees Wax, Benzoic Acid, Olive Oil, White Petroleum, Glycerin and Sodium acetate was provided by Loba chemicals, Mumbai

- **Method:**

Method of preparation of Vildagliptin Cream

- **Preparation of o/w cream formulation**

The aqueous phase and the oil phase are both present in these o/w emulsion-based treatments. The components of oil phase (A) were combined by melting them in a china dish over a water bath at 75 °C while stirring continuously. Separately combined and heated to a temperature similar to that of the oil phase in a beaker, the components of the aqueous phase (B) were prepared. Vildagliptin, which is medicinally effective, is dissolved in aqueous phase. Using an emulsifier, the oil phase was gradually introduced to the aqueous phase whilebeing constantly stirred. The mixture is continuously stirred until cream forms.

Table 1: Batch Formula for Cream Base

Sr. No.	Ingredient	Quantity in gm (10gm)							
		F1	F2	F3	F4	F5	F6	F7	F8
1	Vildagliptin	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
2	Bees Wax	1	0.5	0.5	1	0.5	0.5	0.5	0.5
3	Benzoic Acid	0.5	0.5	1	0.5	0.5	0.5	0.5	0.5
4	Olive Oil	1.5	2	2.5	1.5	1.5	2	1.5	1.5
5	White Petroleum	1.5	0.5	1	1.5	1.5	2	2	2.5
6	Glycerin	1.5	1	1	2	2.5	2.5	1.5	2
7	Sodium acetate buffer	1	1	1.5	-	1	0.5	0.5	0.5
8	Water	q.s. to 10 ml	q.s. to 10 ml	q.s. to 10 ml	q.s. to 10 ml	q.s. to 10 ml	q.s. to 10 ml	q.s. to 10 ml	q.s. to 10 ml

- **Evaluation or Characterization of Optimized Formulation [5-11]**

➢ **Physical examination**

The prepared topical creams were inspected visually for their color, physical appearance, homogeneity, texture, phase separation and feel after the application.

➢ **pH Determination**

Each cream formulation's 50 g weight was placed into a 10 ml beaker, and its pH level was then measured using a digital pH metre.

➢ **Spreadability**

After one minute, the diameter of 1 g of cream between two horizontal plates (2020 cm^2) was measured in order to assess the cream's spreadability. The upper plate was fastened with aregular weight of 125 grammes.

➢ **Viscosity**

The viscosity of the formulations was checked using a Brookfield Viscometer (DV-I PRIME, USA). The creams were rotated at 0.3 rotations per minute. The viscosity of the cream was obtained by multiplying the corresponding dial reading with the factor given in the Brookfield Viscometer catalogue.

➢ **Drug content**

100 ml of buffer were used to weigh, dissolve, and filter 1g of cream before it was run through Whatman filter paper. 1 ml of the sample was pipetted out of the filtrate and diluted withbuffer to make a clear solution in 10 ml. The sample was then examined in a UV spectrophotometer, with the base solution being used as a blank to measure absorbance.

- ***In vitro* diffusion study**

5 grams of cream were evenly distributed over the cellophane membrane. With the stratum corneum towards the donor compartment, the membrane was positioned between the Frantz diffusion cell's compartments. The reservoir compartment was stocked with 100 cc of pH 6.8 phosphate buffer. The trial took place for 412 hours at a temperature of 371 °C with the speed regulated so that the vortex touched the skin. At intervals of 30 minutes, 5 ml of the sample was removed from the reservoir compartment, and absorbance was determined spectrophotometrically at 260 nm. To maintain a consistent volume, 5 ml of phosphate buffer pH 6.8 solutions were periodically added to the reservoir compartment.

- **In-vitro cell line study**

The wound healing capabilities of the sample code A cream was assayed by performing In vitro cell migration studies on L929 cells by a previously described method. Briefly, 2 x 105 cells/mL were seeded in 6-well plates and were cultured overnight. Cells were then washed with Delbucco's Phosphate Buffered Saline (DPBS) and a scratch was made with a sterile 200µL tip. The detached cells and other cellular debris were removed by washing the cells with DPBS. The cells were treated with 1000 µg/mL of sample code A cream and 5 µg/mL of positive control, Cipladine and incubated for 24 h. Cipladine is a standard drug that is used in wound healing. Untreated cells were negative control. The cell migration and morphological changes of cells were observed in the images taken by inverted microscope, equipped with digital camera. The experiments were performed in triplicate (n ¼ 3). The width of the scratch and wound closure at different time intervals (0, 48hrs) was analyzed by SAGLO software.

Result and Discussion:

- **Physicochemical Properties Evaluations**

Table 8.5 lists the physicochemical characteristics of the topical preparations. According to the findings, all of the cream that was developed had good look and homogeneity. The cream was a pale, yellowish white in appearance, and that was its color. The formulations had a seamless texture without any phase separation.

Table 2: Physicochemical Evaluations for different Topical Formulations

Formulation	Color	Physical Appearance	Homogeneity	Texture	Phase Separation	Feel After Application
F1	White	Opaque	Homogeneous	Smooth	No	Film formed after dry
F2	White	Opaque	Homogeneous	Smooth	No	Roughness
F3	White	Opaque	Homogeneous	Smooth	No	Roughness
F4	Yellowish white	Opaque	Homogeneous	Smooth	No	Moisture
F5	Yellowish white	Opaque	Homogeneous	Smooth	No	Moisture
F6	Yellowish white	Opaque	Homogeneous	Smooth	No	Moisture
F7	Yellowish white	Opaque	Homogeneous	Smooth	No	Moisture
F8	Yellowish white	Opaque	Homogeneous	Smooth	No	Moisture

- **pH Determination**

The cream compositions' pH ranged from 5.000 to 6.073 without any active components. When the active components were mixed with the bases, the pH was lowered to 4.80 to 5.05. Normal skin pH levels fall between 4 and 6, which is an acidic range. The skin responded to the cream's formulation as being rather acidic.

Table 3: pH of Formulations With and without Active Ingredients

Formulation	pH (Mean ± SD)	
	Blank	Drug
F1	5.073	5.00
F2	4.073	4.60
F3	5.789	5.05
F4	5.550	4.95
F5	5.150	4.95
F6	5.933	4.90
F7	5.000	4.80
F8	6.073	5.78

- **Spreadability**

F8 Cream has shown more spreadability compared to other cream formulation. The spreadability values indicate that the formulation can easily applied onto the skin.

Table 4: Spreadability of the Cream

Formulations	F1	F2	F3	F4	F5	F6	F7	F8
Spreadability (g cm/sec)	14.2	20.50	24.90	44.47	44.47	50.99	53.60	68.33

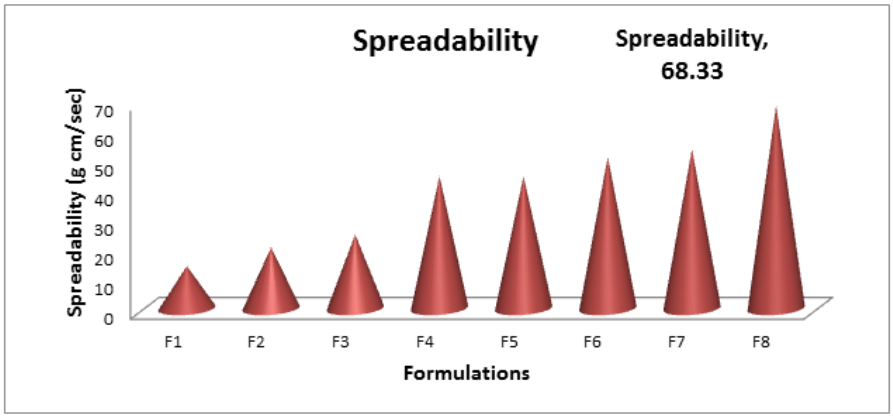

Figure No 1: Spreadability of the Cream

- **Viscosity**

Table 5: Viscosity of the cream

Formulations	F1	F2	F3	F4	F5	F6	F7	F8
Viscosity (Centipoise)	7342	7413	7534	7241	7187	7216	7187	7250

➢ **Drug content**

Drug content of all the formulations are shown in Table 8.8.

Table 6: Drug Content of Prepared Different Formulations

Formulations	F1	F2	F3	F4	F5	F6	F7	F8
Average drug content	3.04±0.130	5.19±0.500	1.18±0.049	9.21±0.140	5.34±0.499	9.34±0.100	9.67±0.4	10.13±0.39

Not all of the formulations displayed the drug content at its theoretical concentration (1 percent w/w). Only F8 demonstrated actual worth. Because there were strong drug entrapment pressures in the semisolid basis, sample F3 had relatively little drug content.

In-vitro drug release study

Formulation F8 showed maximum drug release (24.97%) at 60th min.

Table 7: % Cumulative drug release of Vildagliptin formulations

Time in minute	% Cumulative drug release							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
10	1.50±0.07	1.01±0.13	0.24±0.3	1.54±0.13	1.17±0.10	0.36±0.27	3.83±0.56	5.06±0.67
20	2.24±0.03	1.33±0.05	0.42±0.08	2.83±0.12	1.95±0.12	1.17±0.20	6.33±0.30	8.45±0.32
30	2.91±0.11	2.80±0.06	0.52±0.43	3.81±0.11	3.66±0.16	4.15±0.61	10.37±0.46	13.86±0.97
40	3.21±0.16	3.55±0.04	0.73±0.09	4.17±0.21	4.79±0.08	9.73±0.41	14.40±0.16	17.45±0.34
50	3.60±0.08	4.65±0.05	0.93±0.02	4.46±0.06	5.43±0.22	14.80±0.40	18.98±0.62	26.86±0.41
60	4.51±0.16	6.46±0.09	1.421±0.02	4.52±0.08	6.55±0.11	20.18±0.48	21.51±0.36	24.96±0.61

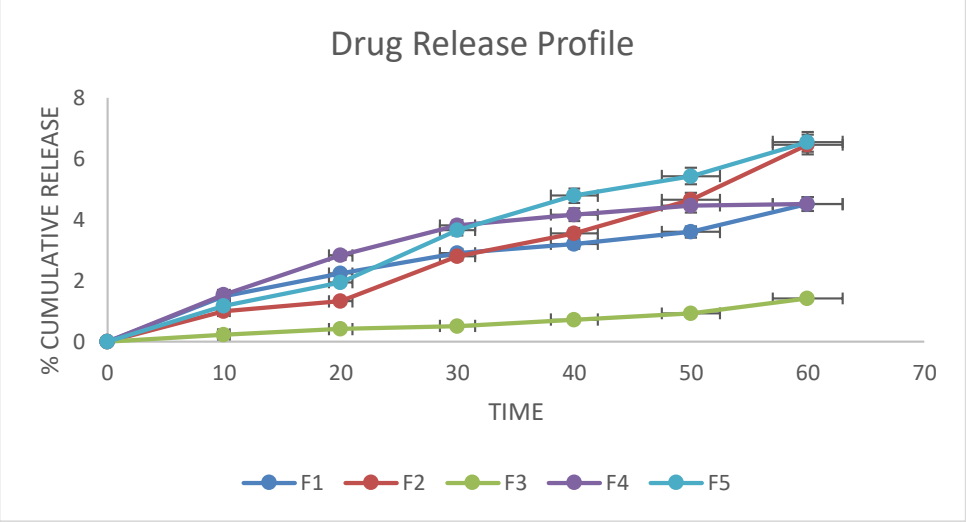

Figure 2 : % Cumulative drug release of Vildagliptin formulations batch F1 to F5

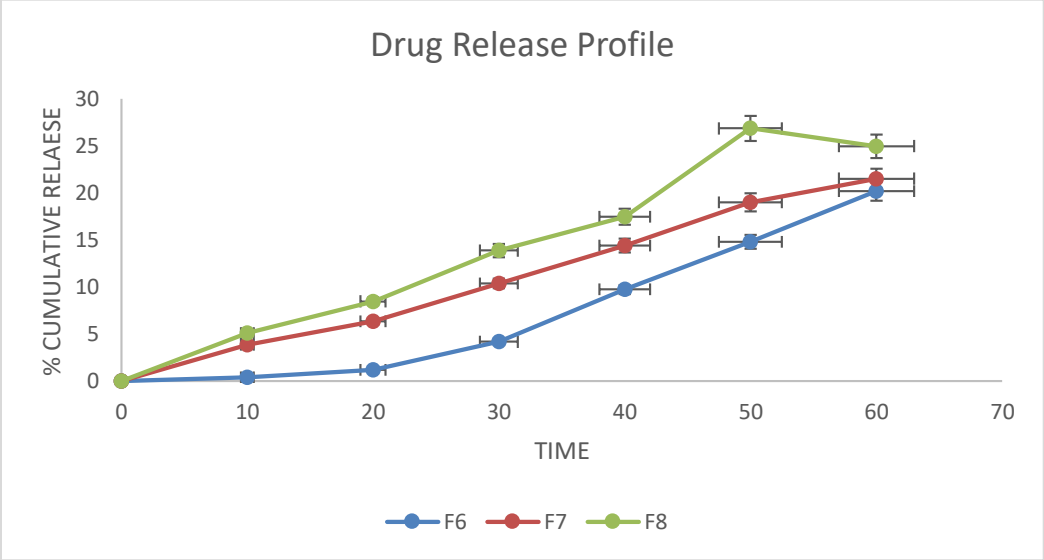

Figure 3: % Cumulative drug release of Vildagliptin formulations batch F6 to F8

➢ In-vitro cell line study

Table 8: Percentage (%) Of Cells Migrated Towards The Wound And Involved In Wound Closure.

Groups	0 hrs (mm)	48 hrs(mm)
Control	00 47	47
Standard cipladine (5 µg/mL)	00	67
Sample code 1 cream	00	46

Microscopical images representing the In vitro wound healing nature of sample code 01 cream: L929 cells were incubated in presence or absence of the sample code. A cream and standard drug Cipladine and images were captured at 0 and 48 hrs.

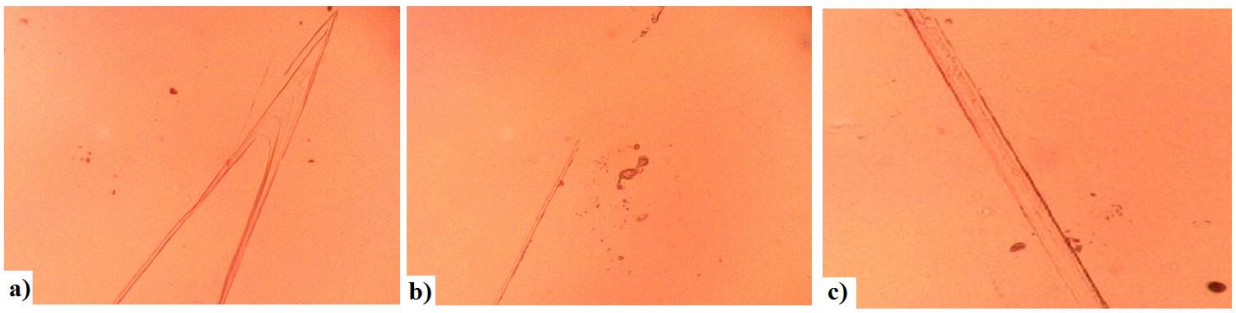

Figure No: a) Control or Untreated, b) Standard (Cipladine), c) Sample Code A Cream (1000 µg/Ml)

Figure 4: a) Control b) Standard cipladine (5 µg/mL) c) Sample code 1 cream

At the concentration (1000 µg/mL), sample code A showed the moderate wound healing activity as compared to standard.

Conclusion

Formulation of cream for wound healing in diabetic patients was successfully developed that met the relevant pharmaceutical characteristics. The prepared formulations showed good spreadability, no evidence of phase separation and good consistency during the study period. Stability parameters like visual appearance, nature, viscosity and pH of the formulations showed that there was no significant variation during the study period. The prepared formulations showed proper pH range that is approximately in the range of pH 4.60 to 5.78; it confirms the compatibility of the formulations with skin secretions. From the present study it can be

concluded that it is possible to develop creams containing Vildagliptin and can be used as the provision of a barrier to protect skin.

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