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Formulation and Estimation of Rapidly Dissolving Sublingual Thin Film of Vildagliptin

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Abstract

The purpose of the present research was to develop a fast and rapidly dissolving polymeric sublingual thin film of vildagliptin due to its simplicity of use as an alternative to oral disintegrating tablets and better compliance for diabetic patients. Nine different formulations (F1-F9) of vildagliptin sublingual films were produced using diverse concentrations of polymer A and plasticizer B by solvent casting method. Several physicochemical properties, including morphological properties, weight variation test, film thickness, folding endurance, surface pH, percentage of moisture loss, *in-vitro* disintegration test, *in-vitro* dissolution test, trinocular microscopic imaging of film, differential scanning calorimetry (DSC), FTIR study and content uniformity were evaluated. The ratios of polymer A-plasticizer B were as follows (5:1), (7:1), (7.67:1), (8:1), (8.5:1), (8.67:1, (9.67:1), (10:1), (11:1) which made the film smooth, mechanically strong and easy to peel out. Among all the different formulations, the F1 formulation showed the most significant result concerning *in-vitro* dissolution (98.95%) in 5 minutes, minimum disintegration time (38 sec.), less film thickness (116.67 ± .58 µm) and better folding endurance (403 times).

Key words: Fast dissolving sublingual film, vildagliptin, anti-diabetic.

Introduction

The oral route is the most popular and effective route of drug administration where both local and systemic delivery of drugs can take place (Mathew, 2015). Many patients, mostly pediatric, geriatric, psychiatric and unconscious patients, face difficulties with the administration of solid dosage forms. Due to the fact that they are afraid of choking, many of these patients do not comply with the administration of solid dosage forms (Kathpalia and Gupte, 2013). Patients who have trouble chewing or swallowing may benefit from the most modern and innovative kind of solid dose, which is fast-dissolving sublingual films. These films are suitable for patients who have these types of issues. It provides rapid onset of action along with providing better bioavailability as it can avoid first pass hepatic metabolic and pre-systemic elimination in the gastrointestinal (GI) tract. When put under the tongue, fast-dissolving sublingual films are engineered and made to disintegrate or dissolve immediately, even within a few seconds, without the need for water. (Jain *et al.*, 2018; Kayastha *et al.*, 2017*;* Gholve *et al.*, 2018, Mostafa, 2018).

Diabetes mellitus (DM) is a chronic, heterogeneous endocrine disorder caused by high levels of glucose in the bloodstream. It was first documented in an Egyptian manuscript about 3000 years ago which was discovered by Georg Ebers in 1862. The distinction between type 1 and type 2 DM was revealed in 1936 (Nwaneri, 2015). According to WHO, it is estimated that diabetes affects approximately 422 million people worldwide, with 46% of diabetic patients being undiagnosed.

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Vildagliptin sublingual films are suitable solid dosage forms as anti-diabetic medication where Vildagliptin is a selective and powerful dipeptidyl peptidase-4 (DPP-4) inhibitor that improves glycemic control by preventing the degradation of both endogenous glucagon-like peptide-1 and glucose-dependent insulinotropic peptide. Vildagliptin was originally developed as a treatment for diabetes (Pan and Wang, 2013). The goal of the current research was to formulate a fast-dissolving polymeric sublingual thin film of vildagliptin that would be easier to use than oral disintegrating tablets and would result in higher patient compliance for people with diabetes.

Materials and Methods

Vildagliptin was received as a gift sample from Drug International Ltd., Dhaka, Bangladesh. Polymer A, plasticizer B, crospovidone, glycerin and citric acid were purchased from Merck, Germany. Distilled water was prepared in the laboratory.

Preparation of vildagliptin sublingual film: The fabrication of sublingual films using the solvent casting process is the most common approach. This method may be used for any medication. Here we used this method for preparing vildagliptin sublingual film (Nair *et al.*, 2015).

Calculation of drug quantity: For 100 mm×100 mm petri-dish, total surface area of petri-dish = (100×100) mm^2 = 10,000 mm^2; Size of individual film = (20×20) mm^2 = 400 mm^2; so, theoretically total number of film per petri-dish = 10000÷400 = 25 pcs. Dose of drug per film = 25 mg; Total amount of drug should be taken in each batch = (25×25) mg = 625 mg.

Preparation of vildagliptin sublingual film by using solvent casting method: By performing the preliminary physical observation of the films prepared the best compositions were used for the incorporation of vildagliptin. Following accurate computation, an adequate quantity of vildagliptin was transferred to a water. After completing the dissolution of the drug, the mixture was stirred with a magnetic stirrer for 30 minutes. Polymer A was taken in another glass beaker and heated to dissolve in distilled water. Then again, a glass beaker, where it was then dissolved in distilled magnetic stirrer is used for stirring it for 45 minutes. After that, plasticizer B and the other components (i.e. glycerin, crospovidone and citric acid) were gradually added and the solution was stirred with the help of a magnetic stirrer for 10 minutes. Finally vildagliptin was added in a specific proportion to the obtained solution. The solution was stirred for 30 minutes and allowed to be kept aside to remove air bubbles. Then the solution was cast onto a glass petri-dish having a surface area of 10,000 mm^2. The film solution was dried with the help of a hot air oven at 50-60°C. After drying, the film was peeled out with the help of a sharp blade. Then the film was cleaved into desired size (20×20 mm^2) and stored in air-tight packets for evaluation. The detailed compositions of the vildagliptin sublingual film formulations which were used in the current study are displayed in table 1.

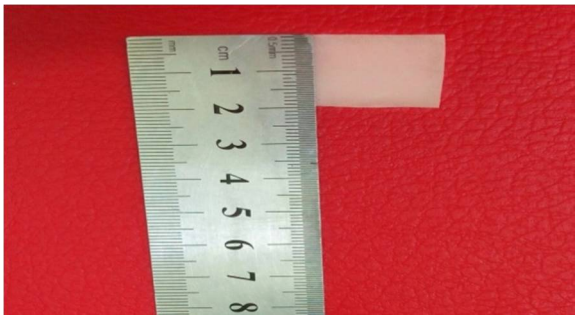

Figure 1. Vildagliptin Sublingual Thin Film.

Evaluation of physicochemical properties

Morphological properties: Visual examination was used to assess the morphological qualities of the oral films, including homogeneity, color, transparency and surface smoothness. The formulations F1 to F6 were white in color, it was soft with the texture of the upper and lower surface of the film being very smooth, F7 to F9 were white, upper and lower surface of the film was rough.

Weight variation test: Three distinct points in the cast film were used as cutting points for the 20x20 mm^2 films. Using an electronic balance, the weight of each film was determined, and after that, the average weight of the film as well as the standard deviation

from the mean was computed. Table 2 presents the findings of the study.

Film thickness: A micrometre screw gauge was used in order to determine the thickness of the film sample. Each 20 by 20 mm^2 film was measured in three distinct spots. A calculation was made to determine the mean thickness as well as the relative standard deviation. Table 2 presents the findings of the study.

Table 1. The composition of vildagliptin sublingual film formulations using different levels of polymer A, plasticizer B and glycerine.

Ingredients	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Vildagliptin (mg)	25	25	25	25	25	25	25	25	25
Polymer A(mg)	25	40	55	70	85	100	115	130	145
Plasticizer B (mg)	5	5	5	10	10	10	15	15	15
Glycerine (mg)	10	10	10	20	20	20	30	30	30
Crospovidone (mg)	8	8	8	8	8	8	8	8	8
Citric acid(mg)	5	5	5	5	5	5	5	5	5
Distilled water (mL)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Table 2. Various physical properties of vildagliptin sublingual films.

Formulation code	Weight variation (mg)	Thickness uniformity (µm)	Folding endurance	Surface pH	% of moisture loss	Disintegration time (sec.)	Content uniformity (%)
F1	55.39 ± 1.01	116.67 ± .58	403 times	8.1	1.05 ± 0.07	38	99.73± 0.92
F2	65.98 ± 0.94	135.67± 1.53	433 times	8.1	1.16 ± 0.08	100	98.63± 0.99
F3	95.72 ± 0.55	203.33 ± 1.15	496 times	8.1	1.28 ± 0.04	140	98.05± 0.99
F4	109.02 ± 0.27	231.33 ± 0.58	548 times	8.1	1.55 ± 0.03	160	96.32± 2.01
F5	123.25 ± 0.47	256.30 ± 0.58	586 times	8.1	1.67 ± 0.05	220	94.67± 1.15
F6	141.44 ± 0.58	343.67 ± 0.58	615 times	8.1	1.88 ± 0.03	360	94.09± 1.86
F7	199.50 ± 0.60	366.00 ± 1.00	743 times	8.1	1.97 ± 0.02	506	94.09± 1.86
F8	229.18 ± 0.26	414.00 ± 1.41	786 times	8.1	2.08 ± 0.07	598	94.09± 1.86
F9	241.65 ± 0.67	436.33 ± 0.58	846 times	8.1	2.14 ± 0.05	627	90.05± 1.93

Note: All the values are expressed as mean ± SD, n =10; SD means standard deviation.

Folding endurance: The number of folds that are required to either break a specimen or create visible fractures is used to represent the folding endurance of a material. The answer was found by repeatedly folding a film with dimensions of 20x20 mm^2 at the same location until it broke. After that, we computed the standard deviation in addition to the mean value of the three measurements. Table 2 presents the findings of the study.

Surface pH study: The films with a surface area of 20x20 mm^2 that were going to be evaluated were put in a petri dish, and then they were sprayed with 0.5 ml of distilled water and allowed to sit for half an hour. A pH meter was used in order to get the pH reading. The results are shown in table 2.

Percentage of moisture loss: One of the parameters that define the hygroscopicity of a film is the amount of moisture that is lost as a percentage. In this particular test, the preliminary weight of a film is recorded, and then the film in question is put into a

desiccator for a period of three days. Desiccator includes calcium carbonate. After a period of three days, the films are removed and their weight is redetermined. The following equation was used to calculate the amount of moisture that is lost. The results are shown in table 2.

Percentage moisture loss = [(initial weight - final weight) / initial weight] × 100

In vitro disintegration test: The moment at which the film begins to break down or disintegrate is referred to as the disintegration time. The *in vitro* disintegration time was visually evaluated by putting a 20x20 mm^2 film in a glass beaker containing 50 ml of distilled water and spinning the mixture every 10 seconds while keeping the temperature at 37±2°C. Table 2 presents the findings of the study.

Content uniformity test: The 20×20 mm^2 film was taken in 100 ml of volumetric flask. A quantity of 60 ml pH 6.8 phosphate buffer was added and sonicated for 30 minutes to dissolve. After that, phosphate buffer with a pH of 6.8 was added to bring the total volume to 100 ml. Utilizing Whatman filter paper, the solution was able to be filtered. After that, 1 ml of the filtrate was removed and diluted to a volume of 10 ml using phosphate buffer with a pH of 6.8. A UV-VIS spectrophotometer was used to determine the absorbance of the solution at a wav elength of 276 nm (Savale, 2018). Table 2 presents the findings of the study.

In vitro dissolution test: For the purpose of the dissolving test, a medium consisting of 600 millilitres of phosphate buffer with a pH of 6.8 was used. The temperature of the medium was kept at 37 ± 2°C. The rotational speed of the gadget was set at fifty. A piece of film with dimensions of 20x20 mm^2 was cut and inserted in the basket. During the course of the experiment, 0.5 ml of samples were taken out at regular intervals of 1 minute for a total of 5 minutes, during which time the same volume of the dissolving medium was replaced with a new phosphate buffer. Phosphate buffer was used to bring the volume of the removed samples up to 10 millilitres. After that, the samples were put through an ultraviolet spectrophotometer set to a wavelength of 276 nm (Savale, 2018). The relationship between time (minute) and percentage of drug release is plotted in the figure 1 where the minimum and maximum % of drug release of F1 to F9 formulations was 40.08% to 98.95% within 5 minutes. However, F1 showed maximum dissolution (98.95%) where thickness was minimum.

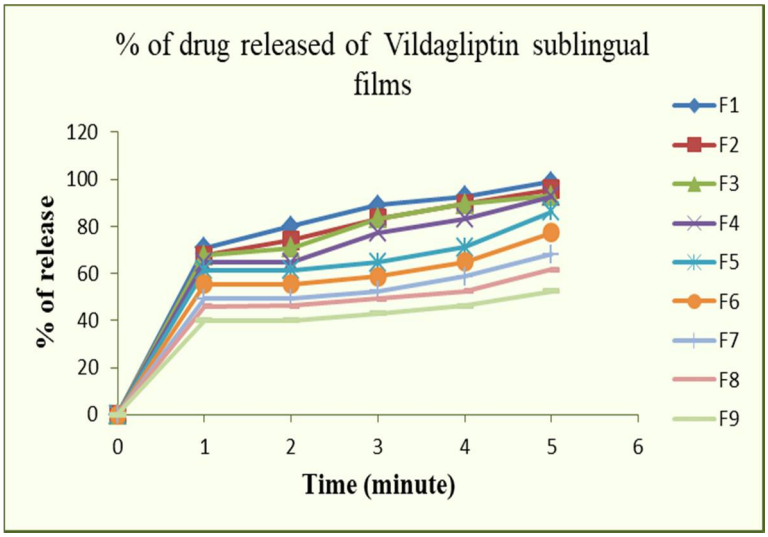

Figure 2. Dissolution test of vildagliptin sublingual films.

Figure 3. Trinocular microscopic image of Vildagliptin sublingual films.

Trinocular microscopic imaging of film: The evaluation of a trinocular microscopic picture of a sublingually applied thin film of vildagliptin was performed using a trinocular digital microscope. We looked at the surface of the film as well as the distribution of the medication and the polymer within the film. It was found smooth surface and uniform drug-polymer distribution. The outcome is shown in figure 3.

Compatibility studies by FTIR spectral analysis: The technology of Fourier transform infrared spectroscopy, also known as FT-IR, was used for the purpose of detecting changes associated with the excipients-drug combination. The disappearance of an absorption peak, a decrease in peak strength, in conjunction with the emergence of additional peaks, is conclusive proof of interactions between the medication and the excipients. For the FTIR studies of films, a small piece of the film was placed gently. The scanning range was 4000-600 cm^{-1}.The FTIR spectra of vildagliptin sublingual film (F1 formulation) showed a slight deviation compared to pure Vildagliptin. The results are shown in figures 4 and 5.

Differential scanning calorimetry: Thermal analysis of pure vildagliptin and Vildagliptin sublingual film of F1 formulation are given in the figures 6 and 7. There is a slight deviation observed between pure vildagliptin and vildagliptin sublingual film of F1 formulation.

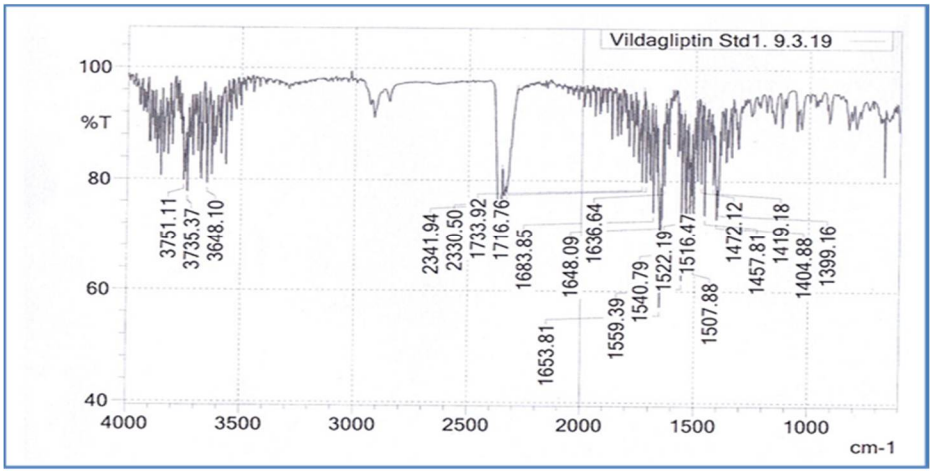

Figure 4. The FTIR spectra of pure vildagliptin.

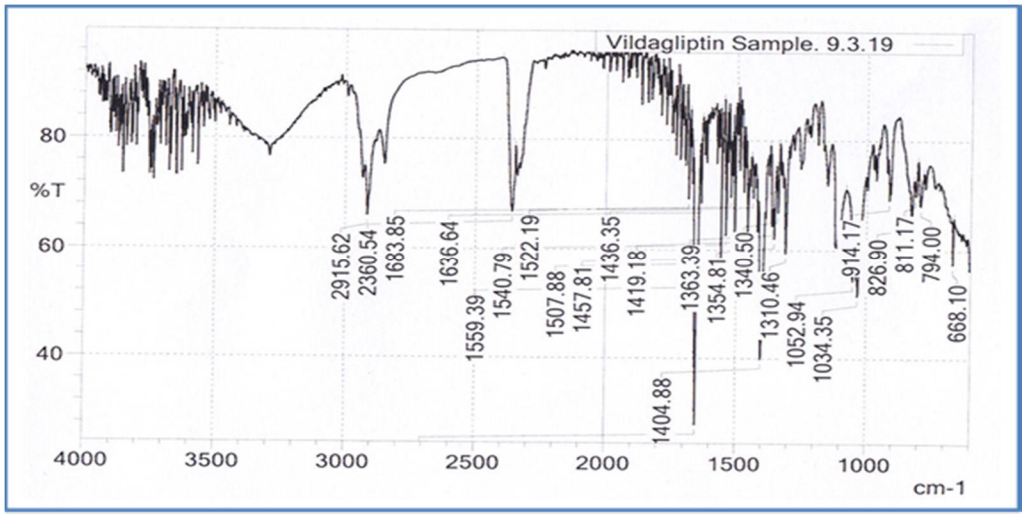

Figure 5. The FTIR spectra of vildagliptin sublingual film of F1 formulation.

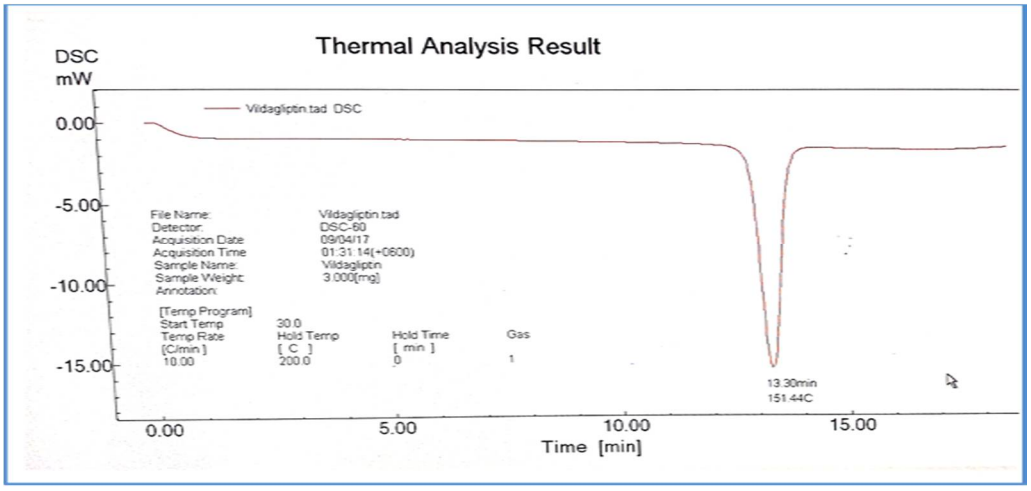

Figure 6. Thermal analysis result of pure vildagliptin sublingual film.

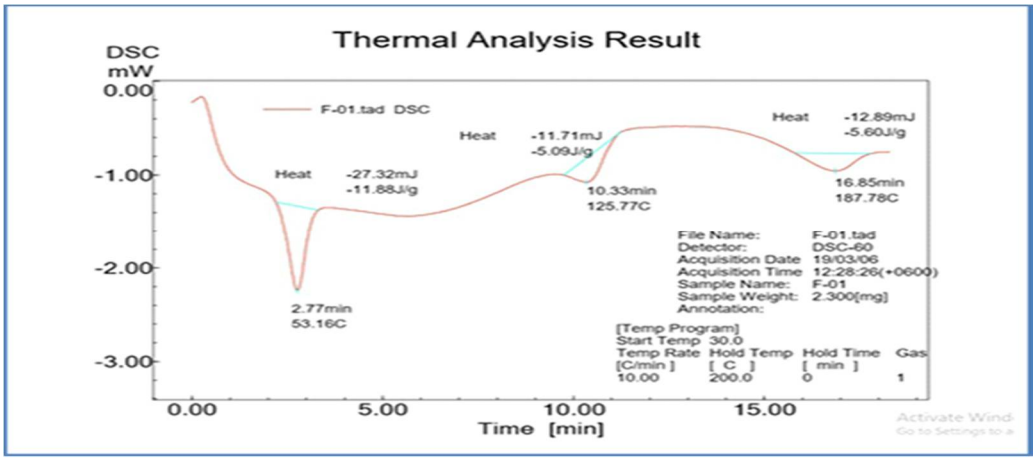

Figure 7. Thermal analysis result of vildagliptin sublingual film of F1 formulation.

Results and Discussion

Total nine batches (F1-F9) of vildagliptin sublingual films were successfully prepared by solvent casting method using vildagliptin as API, polymer A as polymer, plasticizer B as a plasticizer, citric acid as a salivary stimulant, glycerin as a humectant, crospovidone as a super disintegrant and distilled water as solvent where the ratio of the polymer A and plasticizer B were 5:1; 7:1; 7.67:1; 8:1; 8.5:1; 8.67:1; 9.67:1; 10:1; 11:1 respectively. The method was found consistent and reproducible due to the low standard deviation of physicochemical evaluation. The folding endurance and thickness of the film were increased with increasing amounts of polymer A and plasticizer B. Besides, the disintegration time also changes proportionally with the changing concentration of polymer A-plasticizer B. Moreover, the content uniformity of the film was excellent. In this study, it was reflected that, the percentage of drug release was different for different formulations, but the F1 formulation showed good dissolution of film.

Conclusions

Fast-dissolving sublingual films are a revolutionary dosage form for pharmaceuticals over the other conventional dosage form and are reliable for pediatric and geriatric patients. It offers better patient acceptance with painless and simple administration. Evaluating all nine batches of vildagliptin sublingual films, formulation F1 was considered as the best formulation as it showed maximum *in vitro* dissolution (98.95%) in 5 minutes where film thickness (116.67 ± .58 µm) was a minimum. However, advance studies, including FTIR, DSC and stability study are required to confirm the accuracy of this formulation.

Acknowldegement

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Conflicts of interest

There are no competing interests, as the authors have stated.

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