ORIGINAL ARTICLE

Development and in Vitro Evaluation of Multi/bi-bilayer Tablet Dual-release Formulations of Vildagliptin and Dapagliflozin for the Treatment of Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: This study aimed to develop an innovative bilayer tablet formulation of dapagliflozin and vildagliptin to increase therapeutic outcomes and patient compliance in diabetes management. **Methods:** By employing wet granulation, immediate-release, and sustained-release layers were formulated using various super-disintegrating and release-retarding agents, respectively. Several pre-compression parameters were utilized, such as Carr's index, Hausner ratio, physical attributes (weight variations, friability, hardness), and disintegration time. Drug-excipient interactions were determined through employing FTIR, SEM, DSC, and TGA. In-vitro dissolution studies were performed to assess the release kinetics of these formulations. **Results:** For immediate-release dapagliflozin, our earlier study demonstrated that the formulations showed Carr's index (23.5-33.3), physical attributes (weight (145–155 mg), thickness (4.42 ± 0.04 -4.46 ± 0.05 mm), hardness (3.7-5.6 kg/cm^2), friability (<1%), and optimized rapid dissolution (F1: 80.50% ± 5.2 in 30 minutes). For sustained-release vildagliptin, the formulations showed Carr's index (10.48-20), physical attributes (weight (194-203 mg), thickness (3.32 ± 0.06-3.33±0.04 mm), hardness (4.8 ± 0.1-7.6 ± 0.2 kg/cm^2), friability (<1%)), and optimized controlled release (A5: 81.76% ± 2.4 in 360 minutes). The results found that F1 and A5 were the optimum formulation for the immediate release of dapagliflozin, and the sustained release of vildagliptin, respectively, and BT-1 was the optimum bilayer tablet because of its rapid onset of action for dapagliflozin (84.23% within 60 minutes) and sustained release for vildagliptin (80.026% within 360 minutes). **Conclusion:** Based on these data, the optimized bilayer tablet holds the potential to be a convenient and effective treatment option. Further, in-vivo assays are necessary to confirm its efficacy and safety.
Malaysian Journal of Medicine and Health Sciences (2026) 22(1): 1479.1-1479.14.doi:10.47836/mjmhs.v22.i1.1479

Keywords: Diabetes Mellitus, Dipeptidyl peptidase 4 Inhibitors, Sodium-glucose cotransporter-2 Inhibitors, Scanning Electron Microscopy, Fourier transform infrared spectrometry

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INTRODUCTION

Diabetes is a complicated, long-term syndrome connected to numerous metabolic dysfunctions (1). Most of the dysfunctions are brought on by hyperglycemic complications related to insulin secretion, action, or both (1). Diabetes is currently one of the most prevalent chronic illnesses globally, accounting for more than half of all deaths before the age of 70 (2). With an estimated 537 million people affected globally (3), it is a serious global health hazard expected to increase to 783 million by 2045 (4). It is broadly classified into type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes, and several other types originating from monogenic diabetes syndromes and drug or disease- related causes (5). Among the types, T2DM is the most common, comprising 90-95% of all diabetes cases globally, and is characterized by insulin resistance, reduced insulin secretion, and elevated hepatic glucose synthesis. This leads to severe complications, including retinopathy, neuropathy, nephropathy, and cardiovascular disease (6). These complications significantly increase morbidity and mortality rates,

placing a substantial burden on healthcare systems worldwide (6).

Diabetes mellitus, a chronic metabolic disorder, requires a comprehensive management strategy aimed at controlling disease progression, alleviating symptoms, and preventing complications, often necessitating long-term or lifelong pharmacotherapy (7). Effective management of type 2 diabetes mellitus typically necessitates a multifaceted approach that combines lifestyle modifications with pharmacological therapies to improve glycemic control and mitigate complications (8). Pharmacotherapy conventionally involves a range of oral antidiabetic agents, each designed to target distinct pathways involved in glucose regulation. These include biguanides (e.g., metformin), which reduce hepatic glucose production and enhance insulin sensitivity (9); sulfonylureas (e.g., gliclazide), which stimulate insulin secretion but may lead to hypoglycemia and weight gain (10); thiazolidinediones (TZDs) (e.g., pioglitazone), which improve insulin sensitivity but can cause edema and cardiovascular issues (11); alpha-glucosidase inhibitors (e.g., acarbose), which slow carbohydrate absorption but can lead to gastrointestinal side effects (12); dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., vildagliptin), which enhance incretin action to stimulate insulin secretion with a lower risk of hypoglycemia (13); and sodium-glucose cotransporter-2 (SGLT-2) inhibitors (e.g., dapagliflozin), which promote glucose excretion through urine and offer cardiovascular and renal benefits (14). Although all these agents are highly effective medications, many patients may not achieve optimal therapeutic outcomes with monotherapy or single-class treatments (15). Consequently, combination therapy has gained prominence as a strategy to enhance therapeutic outcomes (16). However, a single-layer tablet combining two drugs is impractical due to their distinct pharmacokinetic properties and incompatible release profiles (17). Drugs with varying release characteristics, such as immediate and controlled release, cannot maintain consistent therapeutic concentrations in a single formulation (17).

To address this issue, bilayer tablet technology offers an effective approach to developing dual-release systems capable of delivering medications with distinct release kinetics (18). These formulations consist of two separate layers, each designed to release specific drugs at controlled rates. Notably, bilayer tablets can separate incompatible pharmaceuticals, ensuring that each drug maintains its unique release profile. Besides, a dual-release tablet, incorporating both immediate- and sustained-release characteristics, can align the drug release with the body's circadian rhythm and improve patient adherence (19). Bilayer and multi-bilayer tablet technologies enhance therapeutic effectiveness by retaining distinct release profiles for each layer (20). Hence, combining two drug layers in a single tablet minimizes interactions and ensures optimal release kinetics for both drugs (19). In this study, vildagliptin (a DPP-4 inhibitor) was selected for the sustained-release layer, and dapagliflozin (an SGLT-2 inhibitor) for the immediate-release layer, due to their complementary mechanism of action in the management of T2DM. Vildagliptin enhances the incretin system by prolonging the action of GLP-1, a peptide that mimics glucagon. This mechanism increases insulin secretion and reduces glucagon production during meals (21). Meanwhile, dapagliflozin promotes urinary glucose excretion by inhibiting glucose reabsorption in the kidneys (22). This dual effect not only improves glycemic control but also provides additional benefits, including blood pressure reduction and weight loss. Furthermore, dapagliflozin has been shown to decrease blood pressure and increase water excretion, thereby reducing the risk of heart attacks and heart failure (22).

This study aims to develop and evaluate bilayer tablet formulations for the dual-release administration of dapagliflozin and vildagliptin, specifically targeting enhanced glycemic control in type 2 diabetes mellitus (T2DM) patients. By reducing the pill burden and streamlining the dosing schedule, this study aims to improve patient compliance. Previously, we explored and measured the immediate release properties of dapagliflozin (23). The primary objectives of this study are to design bilayer tablets that incorporate dapagliflozin in the immediate-release layer and vildagliptin in the sustained-release layer, ensuring rapid onset of action while maintaining therapeutic drug levels over a prolonged period. This study also explores the rationale behind excipients selection, their roles in modulating drug release, and the scientific principles governing the formulation of immediate-release dapagliflozin and sustained-release vildagliptin. The focus is on optimizing formulation parameters, including excipient selection, granulation techniques, and compression settings, to achieve consistent reproducibility and maintain drug stability. This research represents a significant advancement in developing treatment options that cater to the specific needs of patients with type 2 diabetes mellitus (T2DM). The ultimate goal of this investigation is to enhance glycemic management and improve patient adherence to therapy, thereby contributing to better clinical outcomes.

It is hypothesized that bilayer tablet formulations, combining immediate-release dapagliflozin and sustained-release vildagliptin, will enhance glycemic control in T2DM patients compared to traditional single-dose formulations. Specifically, the dual-release mechanism will improve therapeutic outcomes by ensuring rapid glycemic control with dapagliflozin while providing prolonged efficacy through vildagliptin, thereby reducing dosing frequency and improving patient adherence.

METHODS AND MATERIALS

Material Source

Active pharmaceutical ingredients (APIs), dapagliflozin, vildagliptin, was obtained from Healthcare Pharmaceuticals Limited. Excipients including crospovidone, sodium starch glycolate, eudragit, L-hydroxypropyl cellulose, magnesium stearate, Avicel 101(MCC), hypromellose, croscarmellose sodium, colloidal anhydrous silica, mannitol, Methocel K4M, Methocel K100M, and Methocel K15M etc. were purchased from authorized local vendors, who import these chemicals from Merck, India.

Fourier-transform Infrared Spectroscopy (FTIR)

A Fourier-transform infrared (FTIR) spectrophotometer (IRSpirit, Shimadzu Corporation, Japan) was used to accomplish FTIR. Approximately 300 mg of potassium bromide (KBr) was weighed and ground to a fine powder. To mix the sample with the KBr, approximately 1 mg of the API or combination of API-excipients was then added and thoroughly ground. Finally, this KBr mixture was pressed and made into a pellet by using an IR press at the pressure of 8 tons. Samples were examined using FTIR on day 0 and after 30 days of storage in order to evaluate potential chemical interactions and stability. The FTIR scans ranged from 4000-600 cm^{-1}.

Formulations Stability and Compatibility Testing

The API and its corresponding mixtures were stored for 30 days in a stability chamber to evaluate possible deterioration and component interactions. The temperature and relative humidity of the chamber were maintained at 25±2 ℃ and 30-65%, respectively.

Thermal Analysis

Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA) were used to perform thermal analysis on a variety of blends and raw materials, such as dapagliflozin and vildagliptin, mixed with maize starch, starch glycolate, croscarmellose sodium, and povidone using DSC250 (Differential Scanning Calorimeter with a 54 position Autosampler and an RCS90 Refrigerated Cooling System, TA Instruments, USA). The analysis was performed at temperatures up to 800 ℃. Each sample was put in a sample holder (a ceramic sample holder for TGA and an aluminum pan for DSC) after being measured to contain a particular amount, ranging from 6 mg to 11 mg. After that, the sample was heated in a nitrogen atmosphere at a rate of 20 °C/min.

Scanning Electron Microscopy (SEM)

The SEM method was employed to visualize each sample's surface structure. The formulation treated with different excipients was examined using a field emission scanning electron microscope (FESEM) (JSM 7610F, JEOL, Japan) at a 15-kV accelerating potential in order to comprehend the morphology of the formed samples. Dried samples were attached to a specimen stub using electrically conductive double-sided adhesive tape or epoxy glue. Prior to analysis, the samples were vacuum-coated with gold in an argon atmosphere.

Formulation and Preparation of Immediate-Release Dapagliflozin

After a thorough review of the literature and in accordance with our earlier study, six super disintegrants such as sodium starch glycolate, crospovidone, croscarmellose-Na, Eudragit, L- hydroxypropyl cellulose, and maize starch were selected to develop the immediate-release dapagliflozin layer. Ten different formulations were created using varying concentrations of those super disintegrants, including the eight formulations (F1–F8) from our earlier study (Table 1) (23-25). Although the amount of mannitol excipients was changed in response to the changes in those super disintegrants, the tablets' overall weight remained unchanged. Each tablet had a final weight of 150 mg and contained 10 mg of dapagliflozin (Table 1). The tablets were formed using the wet granulation process. Initially, the materials were weighed, and Avicel 101 was placed inside a mortar. To create a mucilage, the Avicel 101 was triturated with a pestle and a few drops of water. The remaining components, excluding lubricant and glidant, were then mixed together. The resulting slurry was filtered through a 40-mesh screen. The entire mixture was dried at 30–45 °C as long as the loss on drying (LOD) remained below 5%. The lubricant and glidant were mixed together and then passed through a 20-mesh filter. Particle size was kept small to improve compressibility (26).

Table I: Composition of Immediate-Release Dapagliflozin and Sustained-Release Vildagliptin Tablet Formulations with Different Release-Modifying Excipients

Ingredients	Justification	F9	F10	A1	A2	A3	A4	A5	A6
Dapagliflozin	API	10	10						
Vildagliptin	API	-	-	50	50	50	50	50	50
Crospovidone	Disintegrating agent	-	-	-	-	-	-	-	-
Na-starch glycolate	Disintegrating agent	-	-	-	-	-	-	-	-
Croscarmellose-Na	Disintegrating agent	-	-	-	-	-	-	-	-
Maize Starch	Disintegrating agent	-	-	-	-	-	-	-	-
Eudragit	Disintegrating agent	7.5	-	-	-	-	-	-	-
L- Hydroxypropyl Cellulose	Disintegrating agent		7.5	-	-	-	-	-	-
Methocel K4M	Release retardant	-	-	50	100	-	-	-	-
Methocel K15M	Release retardant	-	-	-	-	50	100	-	-
Methocel K100M	Release retardant	-	-	-	-	-	-	50	100
Mg-stearate	Lubricant	5	5	2	2	2	2	2	2
Colloidal anhydrous silica	Glidant	2	2	2	2	2	2	2	2
Mannitol	Filler	75	75	-	-	-	-	-	-
Avicel 101 (MCC)	Binder	50.5	50.5	96	46	96	46	96	46
Total		150 mg	150 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg

Formulation and Preparation of Sustained-Release Vildagliptin

As suggested by the previous study, six formulations with different ratios of release retardants including Methocel K4M, Methocel K15M, and Methocel K100M —three well-known polymers commonly used in the formulation of sustained-release systems—were selected (27, 28). As with the dapagliflozin formulations, the filler, Avicel 101, was added in varied amounts depending on the disintegration agent amount, while the API level was kept fixed at 50 mg. Similarly, wet granulation and tablet formulation techniques of dapagliflozin were applied to produce sustained-release vildagliptin tablets. The lubricant and glidant were carefully combined, and the resulting mixture were then run through a 20-mesh filter to get the ideal particle size for compression (Table 1).

Formulation and Preparation of Bilayer Tablets of Dapagliflozin and Vildagliptin

Several bilayer tablets were formulated and created by combining 150 mg of immediate-release dapagliflozin and 200 mg of sustained-release vildagliptin, using Flexitab Tablet Press (Lab Press-Pilot 200DL, Shakti Pharmaceutical Private Limited, India) from Beximco Pharmaceuticals Limited. Both immediate-release and sustained-release blends were separately and precisely weighed. Three optimized formulations of immediate-release dapagliflozin and sustained-release vildagliptin were prepared, BT-1 (A3 + F10), BT-2 (A5 + F9), and BT-3 (A1 + F4), and subjected to direct compression techniques.

Physical Parameters

Weight and Weight Variability

The mean mass of 10 tablets was determined, and they were then weighed separately to get the standard deviation, using an Analytical Balance (Model: PS.P3.610 Pscale, Taiwan). Each tablet was weighed individually to the nearest milligram. To assess the weight variability, the standard deviation was calculated from the individual weights of the ten tablets. The weight uniformity was then evaluated by comparing the results to the pharmacopeial limits for uniformity of dosage units.

Thickness

Tablets (10 randomly chosen) were evaluated for thickness using a Digital Vernier Caliper (Model: 500-196-20, Mitutoyo Corporation, China). Each tablet was placed on a flat surface, and the caliper was used to measure the thickness at three different points: one at the center and one on each side of the tablet. The measurements were recorded to the nearest 0.01 mm. The mean thickness was calculated by averaging the three measurements for each tablet. The standard deviation was also calculated to assess the consistency of tablet thickness.

Hardness

Hardness was assessed by Monsanto Hardness Tester (MHT-20, Campbell Electronics, India). Ten randomly selected tablets were placed in the tester, and the force required to break each tablet was measured. The hardness was recorded in kilograms (kg) as the force required to fracture the tablet. The average hardness for the ten tablets was calculated, and the standard deviation was determined to assess uniformity in tablet hardness.

Friability

Ten tablets were randomly selected and placed in the drum of the Friability Tester (EF-2L, Electrolab Private Limited, India) which was then set to rotate for 100 intervals over 4 minutes. The tablets were allowed to remain motionless until they reached equilibrium. The percentage of weight loss was then determined.

% F = {1-(Wt. /W)} *100

Where, % F = Friability in %, W= Initial weight of tablets, Wt. = weight of tablets after the revolution.

In-vitro Disintegration Test

The Disintegration Tester (ED-2L, Electrolab, India) was used to test disintegration in distilled water media at 37 ± 2°C. After the tablets were placed inside the container, the machine was operated at a speed of 30 strokes per minute. The tablets were monitored until either all of them disintegrated or there were pieces that couldn't be broken apart. Both 0.1 N HCl and 6.8 pH phosphate media were prepared to analyze the immediate-release tablets and sustained-release tablets. In general, the time limitation for disintegration of immediate-release tablets is 3-5 minutes, whereas the time limit for sustained-release tablets is 30 minutes (24). Both 0.1 N HCl and 6.8 pH phosphate media were prepared to analyze the immediate-release tablets and sustained-release tablets (23).

Preparation of the Standard Curve of Immediate-Release Dapagliflozin and Sustained-Release Vildagliptin

A standard calibration curve for immediate-release dapagliflozin in 0.1N hydrochloric acid (HCl) and for sustained-release vildagliptin in both 0.1N HCl and pH 6.8 phosphate buffer was constructed. To prepare the dapagliflozin curve, 100 mg drug was dissolved in 100 mL of 0.1N HCl, followed by a 10-fold dilution, resulting in concentrations of 0, 2, 4, 6, 8, and 10 µg/mL. Absorbance was recorded at 224nm, using a Spectrophotometer (EMC-61PC-UV, EMCLAB Instruments GmbH, Germany) (23, 29). For the immediate release of dapagliflozin, the calibration curve obtained was expressed by the equation y = 0.0512x + 0.0149 with an R^2 value of 0.9909. Besides, due to the sustained-release properties of vildagliptin, two calibration curves were generated. In 0.1N HCl, 100 mg vildagliptin was dissolved in 100 mL, similarly diluted, and concentrations ranging from 0 to 10 µg/mL were prepared, with absorbance measured at 210 nm (27). In pH 6.8 phosphate buffer, 10 mg vildagliptin was dissolved in 100 mL of buffer, followed by serial dilutions to achieve concentrations of 4, 8, 12, 16, and 20 µg/mL. Absorbance for the phosphate buffer was measured at 210 nm (27). These calibration curves provided the necessary reference for subsequent quantitative analysis. For sustained-release vildagliptin, the calibration curve in 0.1N HCl media was expressed by y = 0.0137x + 0.0029, with an R^2 value of 0.9907. In the pH 6.8 buffer media, the equation was y = 0.0132x + 0.0002, and the R^2 value was 0.997.

In-vitro Dissolution Study

Using appropriate dissolution media, apparatus, and Dissolution Tester (Inspire-08, Electrolab, India), in-vitro dissolution study was conducted for immediate-release dapagliflozin, sustained-release vildagliptin, and bilayer tablets. For dapagliflozin, dissolution was performed in 0.1N hydrochloric acid (HCl) using a USP type II apparatus with a paddle rotating at 50 rpm and a maintained temperature of 37±0.5 °C. Samples were collected at intervals of 15, 30, 45, and 60 minutes, and the medium was replenished after each sampling. Absorbance was measured at 224 nm (23, 29). For sustained-release vildagliptin, a similar type II apparatus was used with a pH 6.8 phosphate buffer as the medium. The study was conducted over 6 hours, with samples taken at 5, 10, 15, 30, 45, 60, 90, 120, 180, and 360 minutes. After each sample, 5 mL of fresh buffer was added to maintain the volume. Absorbance was measured at 210 nm (27). The dissolution of bilayer tablets, containing both immediate- and sustained-release layers, was studied in both 0.1N HCl and pH 6.8 phosphate buffer. Samples for the immediate-release layer were taken at 5, 10, 20, 30, 45, and 60 minutes in HCl, while samples for the sustained-release layer were collected at 30, 60, 90, 120, 180, 240, 300, and 360 minutes in the phosphate buffer, with the media replenished after each sampling.

Statistical Analysis

Statistical analysis was conducted using Microsoft® Excel® 2016 MSO (Version 2405 Build 16.0.17628.20006) 32-bit. All in vitro analysis were performed three times and expressed as mean ± standard deviation (SD).

RESULTS

Compatibility Assays of API and Polymers

Fourier-transform Infrared Spectroscopy (FTIR):

The usual bands of O–H, C=C, aromatic C–O, O–H, C=O, and C=C groups were seen in pure dapagliflozin. Absorption peaks for pure dapagliflozin were observed in the FTIR spectra at 1247.51 cm^{-1} (C–O ester stretching), 1512.18 cm^{-1} (C=C, aromatic), and 3359.12 cm^{-1} (O–H stretching) (29, 30). Peaks for dapagliflozin

and formulations F1–F8 were previously reported (23), while F9 and F10 formulations aligned with reference peaks (Figure 1(a), 1(b)). The physical mixing of the drug, super disintegrants, and other excipients did not significantly alter its absorption bands in the FTIR spectrum, indicating that no chemical interactions occurred between the medication and the excipients in solid form. Typical FTIR peaks for pure vildagliptin include 3292.49 cm^{-1}(N-H stretching), 2812.51 cm^{-1}(C-H stretching), 2848.86 cm^{-1} (O-H stretching), 1653 cm^{-1} (C=O stretching), and 1465 cm^{-1} (CH_2 bending) (31). Corresponding functional groups showed similar peak values, such as N-H stretching at 3294.42 cm^{-1}, C-H stretching at 2852.72 cm^{-1}, O-H stretching at 2916.37 cm^{-1}, C=O stretching at 1658.78 cm^{-1}, and CH_2 bending at 1408.04 cm^{-1}, indicating consistency within the expected range for vildagliptin. In the spectra of three formulations of vildagliptin, the wave number of those formulations having vildagliptin indicates a similar value (Figure 1(c)). No significant changes in the number of peaks or wavelength range were observed across all prepared formulations, including A1, A3, and A5 (Figure 1(d), 1(e), 1(f)). Similarly, in the bilayer tablet, the peak number and wavelength for both dapagliflozin and vildagliptin remained consistent with those of the individual drugs (Figure 1(g), 1(h), 1(i)). These results indicate the absence of any chemical interaction between the drugs and excipients, both in their pure forms and within the mixture, and stability was maintained over the 30-day testing period.

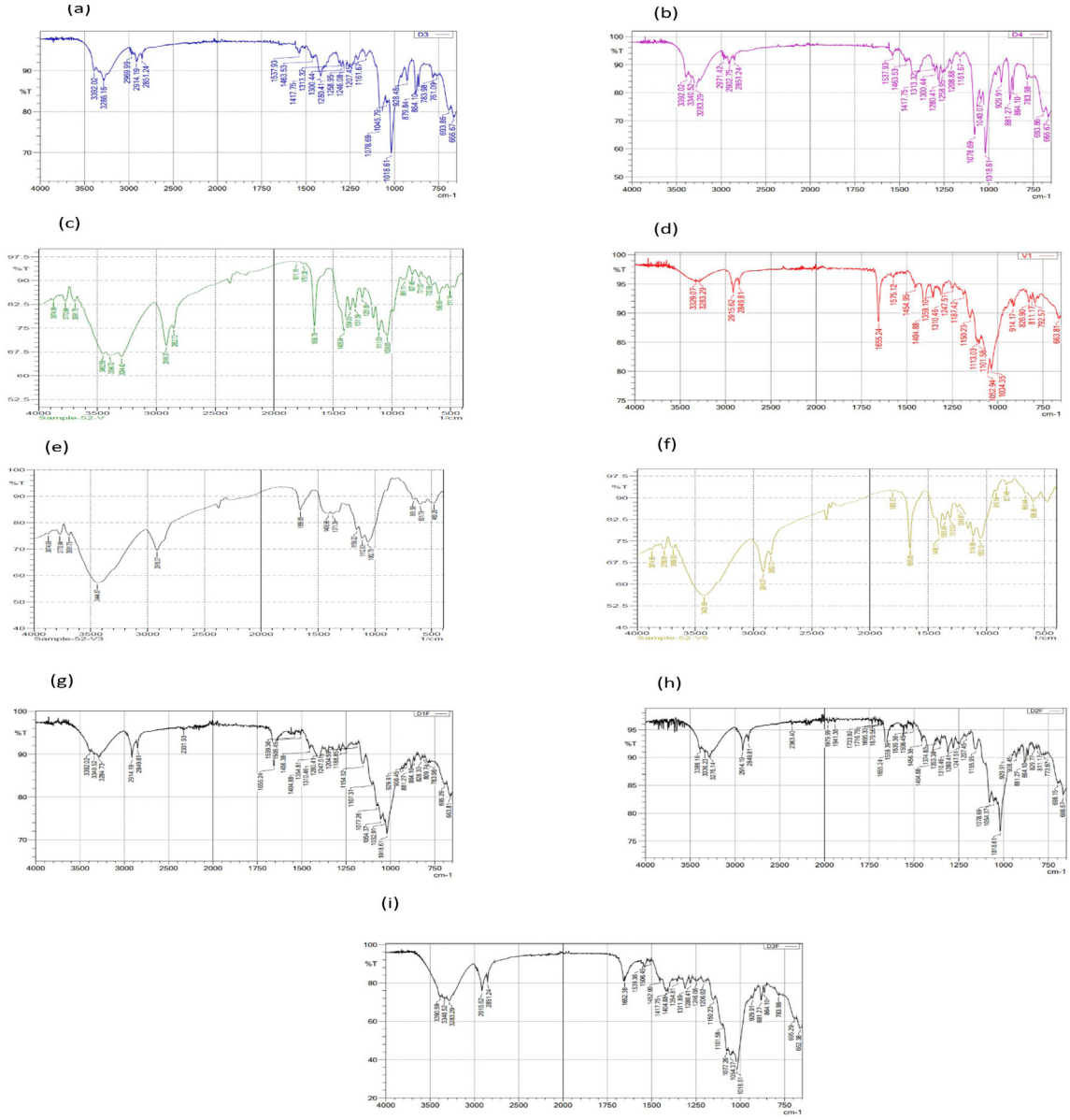

Figure 1: FTIR spectra of various formulations and raw materials.
The FTIR spectrum of (a) formulation F9, (b) formulation F10, (c) raw vildagliptin, (d) formulation A1, (e) formulation A3, (f) formulation A5, (g) bilayer tablet BT-1, (h) bilayer tablet BT-2, and (i) bilayer tablet BT-3 are presented. Characteristic peaks representing key functional groups and their vibrational modes are annotated for each sample. These spectra highlight the molecular interactions and compatibility among excipients and active pharmaceutical ingredients in the formulations.

Thermal Analysis:

The thermodynamic behavior of dapagliflozin and vildagliptin along with the excipients were performed using TGA and DSC (Figure 2). The thermal analysis of dapagliflozin formulations was previously reported (23). Figure 2(a) presents the TGA and derivative thermogravimetric (DTG) curves for the sustained-release vildagliptin formulation. The DTG curve highlights a prominent degradation peak at approximately 201.5 °C, corresponding to the primary thermal decomposition event of vildagliptin in the sustained-release matrix. This peak indicates a rapid breakdown of the active ingredient and matrix components at elevated temperatures. Beyond 250 °C, the weight loss continues but at a reduced rate, suggesting that the majority of thermally sensitive components have decomposed.

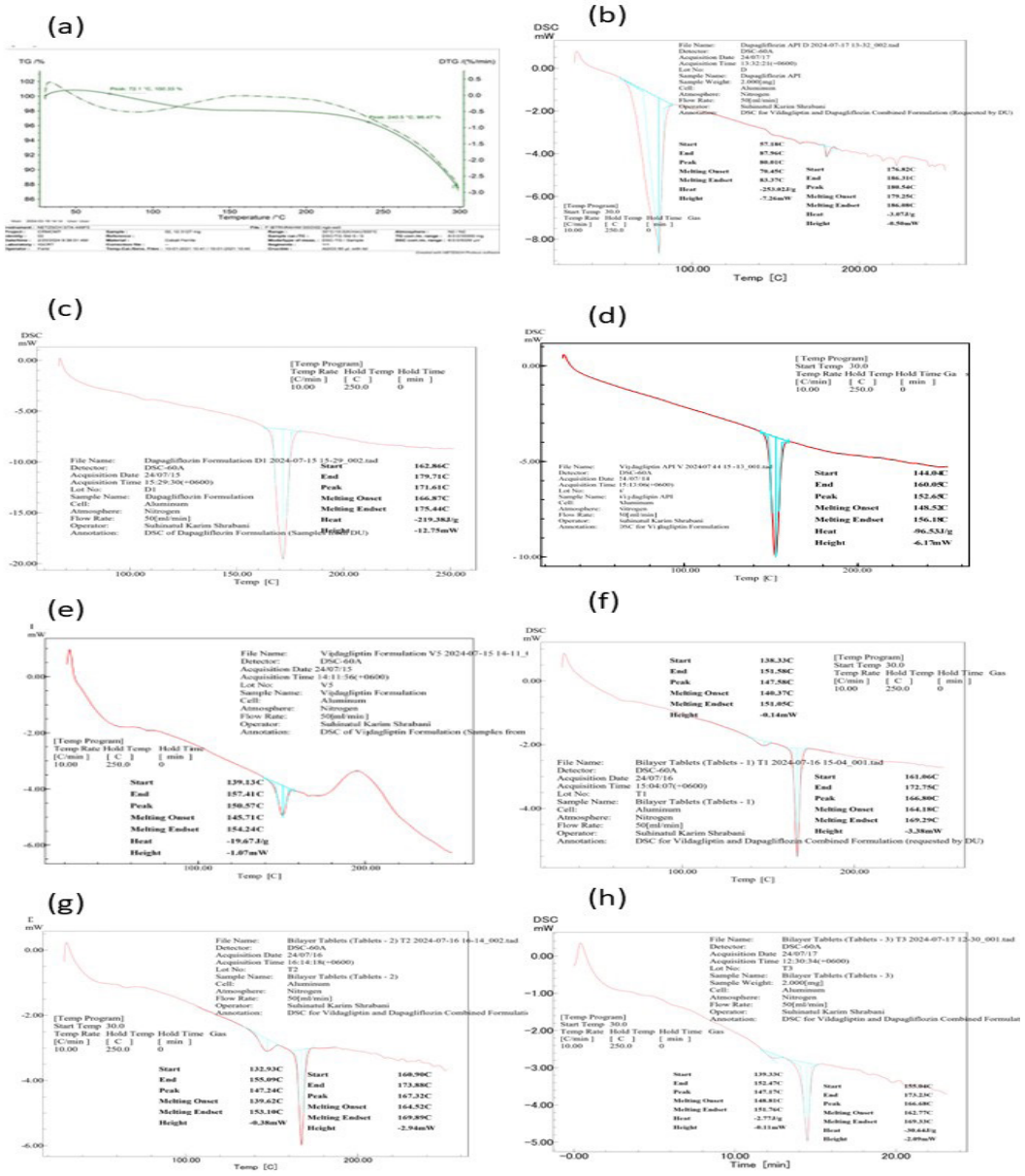

Figure 2: Thermal analysis of formulations and raw materials.

(a) TGA curve of sustained-release vildagliptin formulations showing weight loss as a function of temperature. DSC curves of (b) dapagliflozin raw material, (c) F5 formulation, (d) vildagliptin raw material, (e) A5 formulation, (f) bilayer tablet BT-1, (g) bilayer tablet BT-2, and (h) bilayer tablet BT-3. The thermal events, including melting points, peak transitions, and endothermic/exothermic behaviors, are annotated for each sample, providing insights into their thermal stability and compatibility.

Differential Scanning Calorimetry (DSC) analysis was conducted to assess the thermal characteristics of raw materials and different formulations. The DSC analysis of dapagliflozin API revealed two distinct melting regions, indicating the presence of polymorphs (Figure 2(b)). The first transition occurred at lower temperatures (70.45 °C to 83.37 °C) with an enthalpy of -253.02 J/g, suggesting a polymorphic transformation and the existence of a metastable form that could influence the drug's solubility. The second melting transition at higher temperatures (179.25 °C to 186.08 °C) had a much lower enthalpy (-3.07 J/g), representing the complete melting of the crystalline structure. In formulation F5, a single, well-defined melting region (166.87 °C to 175.44 °C) was observed with an enthalpy of -219.38 J/g, indicating that the excipients stabilized the crystalline form and prevented the polymorphic transition (Figure 2(c)). Besides, the pure API of vildagliptin exhibited a sharp melting onset at 148.52 °C, with a peak at 152.65 °C and an enthalpy of -96.53 J/g, indicating a well-defined crystalline structure with minimal impurities (Figure 2(d)). Formulation A1 showed a reduced melting onset at 145.31 °C and peak at 150.67 °C, with a significantly lower enthalpy of -15.15 J/g, suggesting reduced crystallinity due to drug-excipient interactions. Formulation A5 displayed a melting onset at 145.71 °C, a peak at 150.57 °C, and an enthalpy of -19.67 J/g, reflecting a moderate reduction in crystallinity and thermal stability, potentially offering a more controlled release profile (Figure 2(e)).

The DSC profile of Bilayer Tablet (BT-1) revealed two distinct thermal events: the first occurred at a lower temperature range (melting onset 140.37 °C, peak 147.58 °C, and enthalpy -0.14 mW), indicating a possible interaction between vildagliptin and excipients, while the second event (onset 164.18 °C, peak 166.80 °C, enthalpy -3.38 mW) corresponded to the melting of dapagliflozin, suggesting that both drugs maintained their crystalline structures (Figure 2(f)).

BT-2 displayed similar thermal events but with a slight increase in the end set temperature (153.10 °C), implying marginally increased crystallinity for vildagliptin, with consistent thermal behavior for dapagliflozin (Figure 2(g)). In BT-3, the DSC profile showed a higher enthalpy (-2.77 J/g) for vildagliptin, indicating increased crystallinity, while dapagliflozin exhibited a melting onset of 162.77 °C and significantly higher enthalpy (-30.64 J/g), suggesting a slower dissolution rate and prolonged release (Figure 2(h)). Overall, BT-3's higher crystallinity could enhance thermal stability but potentially reduce solubility and bioavailability, requiring excipient adjustments to optimize drug release. The thermal events observed in the DSC and TGA curves (Figure 2) exhibit minor shifts in onset, peak, and endset temperatures. These variations are within acceptable ranges and do not suggest significant drug-excipient interactions (32). The melting points of dapagliflozin and vildagliptin in the combined formulations showed minimal variation when compared to their pure forms. The observed shifts can be attributed to slight variations in sample composition, particle size, or distribution within the matrix. No new endothermic or exothermic peaks were observed, indicating the absence of new chemical entities or degradation products (32). Therefore, the stability of the drugs is maintained. Long-term stability studies and dissolution profiling are essential for a thorough evaluation of any subtle effects on drug release over time.

Scanning Electron Microscopy:

The micrographs of the dapagliflozin immediate-release layer were previously reported (23). The surface texture of vildagliptin is more consistent than that of dapagliflozin, suggesting a fine powder or micro-crystalline composition (Figure 3(a),3(b)). The presence of pores and voids in figure 3(b) is evident, perhaps facilitating improved wettability and an accelerated drug release profile. This microstructure corresponds with the instant release goal, facilitating fast absorption. The pictures (BT-1) show smooth and compact surfaces, indicative of sustained-release matrices (Figure 3(c)). These layers have fewer fissures, signifying less porosity, which aids in regulating drug diffusion and extending the release time. The densely arranged structures (BT-2) indicate the existence of polymers or excipients that regulate the hydration and gelation processes, essential for prolonged drug release (Figure 3(d)). The interfacial layers of vildagliptin and dapagliflozin may exhibit variations in swelling and erosion characteristics, influencing the release kinetics of the bilayer system (BT-3) (Figure 3(e)). These data validate the structural stability of the bilayer tablet, endorsing its potential effectiveness in dual drug release for diabetes therapy.

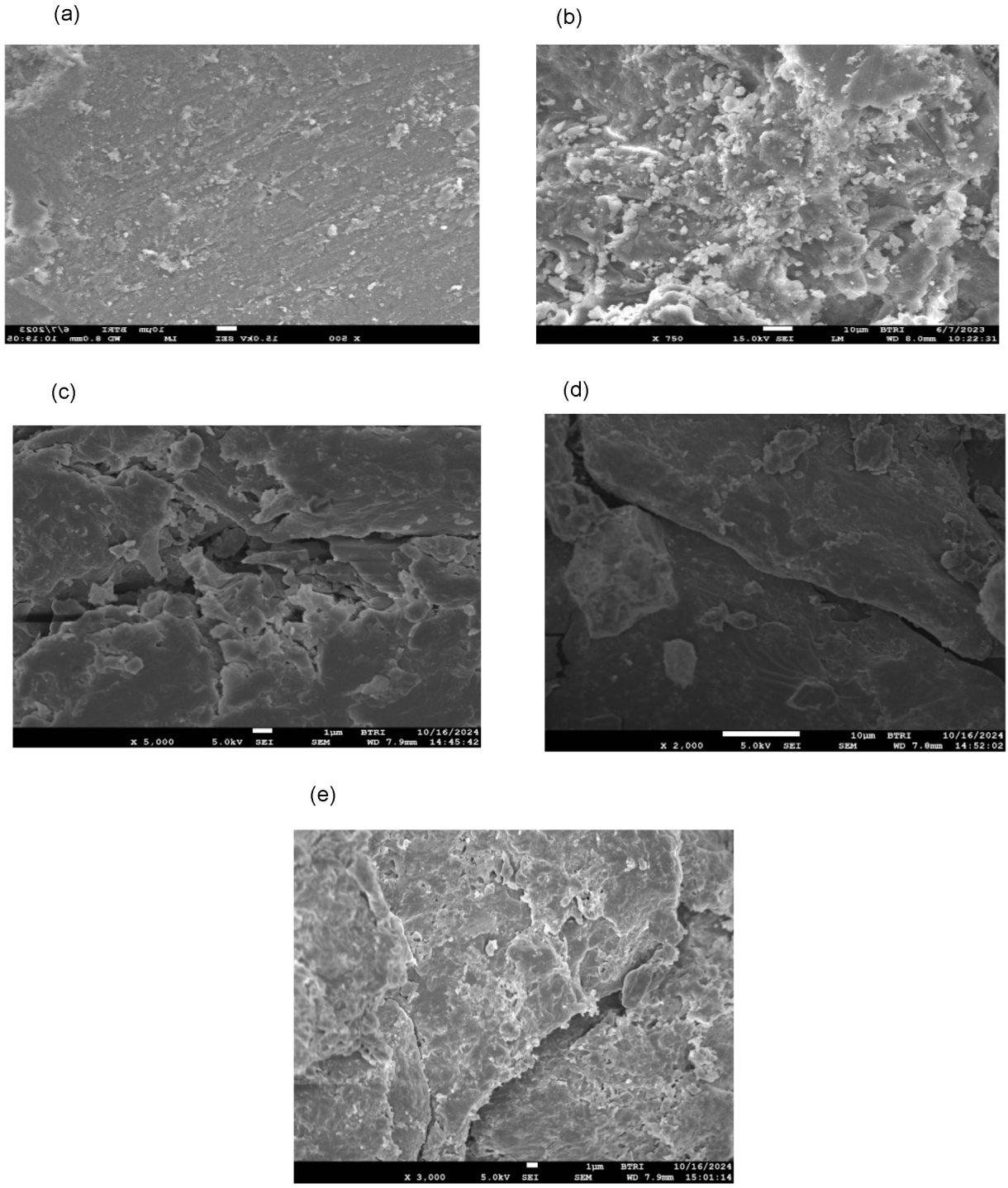

Figure 3: Scanning electron microscopy (SEM) images of the formulated tablets and raw materials.
(a), (b) SEM micrographs of vildagliptin sustained-release layer, highlighting the matrix structure. (c) SEM micrograph of bilayer tablet BT-1, (d) bilayer tablet BT-2, and (e) bilayer tablet BT-3, illustrating the surface characteristics, layer integration, and potential porosity of the bilayer formulations.

Characterization Parameters of Immediate-Release Dapagliflozin Formulations and Sustained-Release Vildagliptin:

The pre-compression and post-compression characteristics, including Carr's index, Angle of Repose, Hausner's Ratio, Friability, Hardness etc. were determined for sustained-release vildagliptin (Table 2). The characteristics of dapagliflozin immediate-release layers were reported in our previous study (23). The investigation revealed that the average weight of sustained-release vildagliptin layers ranged from 194 to 203 mg, with a thickness of 3.32 ± 0.01 to 3.33 ± 0.04 mm, hardness between 4.8 and 7.6 kg/cm^2, and friability ranging from 0.53% to 0.83%. Formulation F7 of immediate-release dapagliflozin has the shortest disintegration time of 1 min 10 sec (23), and A2 of sustained-release vildagliptin has the highest disintegration time of 25 min 6 sec (Table 2). These disintegration times align with existing guidelines, which recommend that immediate-release tablets should disintegrate within 5 minutes to ensure rapid drug release, while sustained-release formulations should exhibit slower disintegration to provide prolonged release and minimize fluctuation in drug plasma levels (24).

Table II: Pre-compression and Post-compression Evaluation Parameters of Sustained-Release Vildagliptin Tablet Formulations

Formulation	Carr's Index	Hausner Ratio	Angle of repose	Average weight (mg)	Thickness (mm)	Friability (%)	Hardness (kg/cm^2)	Disintegration Time
Sustained release Formulations of Vildagliptin								
A1	19.5	1.22	29.4	198	3.32±0.05	1.02±0.04	4.8±0.1	20min 12sec
A2	20	1.25	33.2	194	3.33±0.04	0.87±0.01	7.6±0.2	25min 6sec
A3	14	1.19	30.11	196	3.33±0.03	0.73±0.05	6.2±0.3	15min 19sec
A4	10.48	1.11	28.2	201	3.32±0.01	0.76±0.02	5.8±0.2	17min 11sec
A5	12.05	1.16	27.5	202	3.32±0.06	0.53±0.02	5.2±0.5	19min
A6	11.86	1.15	32.24	203	3.33±0.02	0.67±0.01	6.3±0.6	23min 20sec

Dissolution Study of the Immediate-Release Dapagliflozin and Sustained-Release Vildagliptin:

The study evaluated the drug release profiles of immediate-release dapagliflozin and sustained-release vildagliptin formulations. Our earlier study demonstrated that the F1 formulation containing crospovidone had the fastest and highest drug release (23). The drug release profile of the F1 formulation in this study is substantially higher than that of the F9, F10, pure drug, and the commercially available product (Figure 4(a)) (23, 33). Besides, the pure drug vildagliptin showed 100% drug release within 45 minutes, which was also mentioned by previous studies (34). For sustained-release vildagliptin layer, the drug release patterns showed that A2 has the fastest release profile, while A4 has the slowest, compared to other formulations within 45 minutes. However, due to physical stability issues, A5 formulation with Methocel K100M was selected as the optimal formulation, offering a balanced friability, hardness, and disintegration time as well as a sustained-release profile with over 80% drug release at 6 hours (Figure 4(b)).

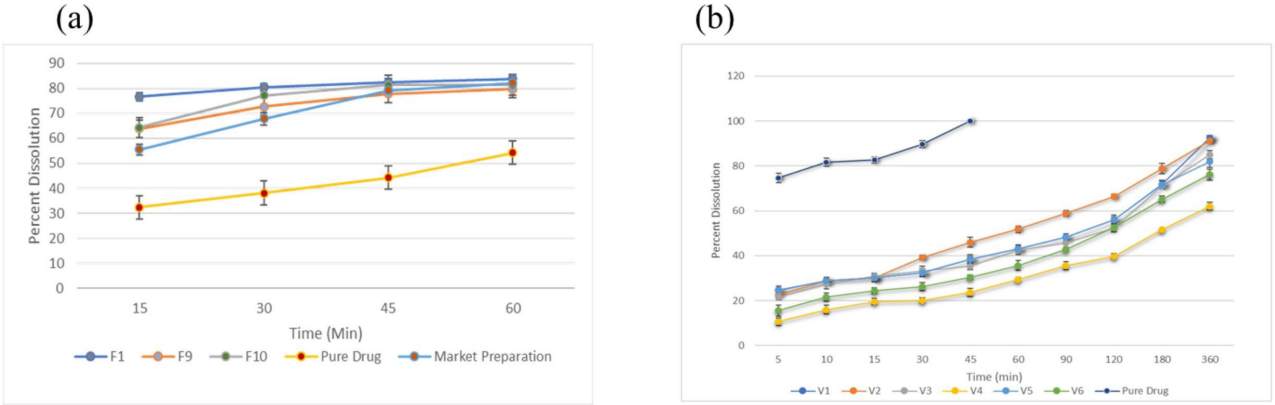

Figure 4: Percent drug release of formulations. (a) Immediate-release dapagliflozin formulations (F1, F9, F10), pure dapagliflozin, and marketed preparation; (b) vildagliptin sustained-release formulations (V1–V6) and pure drug. Drug release profiles were evaluated over time under specified conditions, highlighting the enhanced release characteristics of optimized formulations compared to the pure and marketed drugs. Data are expressed as means ± SD (n = 3).

Dissolution Study of the Bilayer Tablet:
Dissolution studies were performed to evaluate the release profiles of three bilayer tablet formulations, BT-1, BT-2, and BT-3. For immediate-release layers within 60 minutes, BT-1 exhibited dissolution rates of approximately 84.23%, which is equivalent to the optimum immediate-release formulation of dapagliflozin, F1 (Table 3). However, BT-2 and BT-3 showed lower rates of drug release kinetics. For the sustained-release phase, at 360 minutes, BT-1 displayed dissolution rates of around 80%, which is almost equivalent to the optimum sustained-release formulation of vildagliptin, A5. So, BT-1 is recommended as the optimized bilayer tablet because of its desirable dissolution profile for both the immediate and sustained-release layers.

Table III: In-Vitro Dissolution Profiles of Immediate-Release and Sustained-Release Layers of Bilayer Tablets.

Time (Min)	Percentage Dissolution (Immediate- release layer)			Time (Min)	Percentage Dissolution (Sustained- release layer)		
	BT-1	BT-2	BT-3		BT-1	BT-2	BT-3
5	41.5	39.89	25.3	30	28.12	26.028	30
10	58.45	54.01	41.23	60	41.86	39.73	38.024
20	64.43	66.63	49.03	90	49.034	48.64	47.5
30	73.9	73.9	57.6	120	60.192	58.2	56.046
45	79.6	77.12	60.94	180	70.82	68.7	67.08
60	84.23	78.03	61.86	240	76.4	74.41	75.644
				360	80.026	77.532	75.94

DISCUSSION

The study sought to investigate the immediate-release properties of dapagliflozin and the sustained-release properties of vildagliptin. Inhibitors of DPP-4 (e.g., vildagliptin) and SGLT-2 (e.g., dapagliflozin) are often used to treat Type-2 Diabetes Mellitus worldwide, and when used together, they may have cardioprotective benefits through mitochondrial fission (35). SEM analysis (Figure 3) revealed that immediate-release dapagliflozin particles are mostly spherical, with size variability and considerable clumping. On the other hand, sustained-release vildagliptin with Methocel content illustrated an intact, smooth surface, without any indications of openings, channels, or depressions in the molecules. Crystallinity and amorphous transition regulate the release of vildagliptin from the suggested matrix tablets.

FTIR spectral analysis (Figure 1) and Thermograms (Figure 2) demonstrated no interactions among dapagliflozin, vildagliptin, excipients, and polymers. The primary peaks of both medications were preserved in the FTIR data, which indicated chemical compatibility and no interference with functional groups(30). This is very crucial for maintaining the therapeutic efficacy and safety of the drug, as well as ensuring the integrity of the formulation. Besides, thermograms further affirmed this by showing no substantial alterations in the endothermic peaks of the drug in mixture samples, ensuring its therapeutic efficacy and stability throughout the shelf life of the formulation (36).

Dapagliflozin has a half-life of 12.9–13.8 hours (10–50 mg doses) with 91% protein binding, while vildagliptin has a half-life of 2–3 hours (IV to oral) with 9.3% protein binding, advocating for its immediate-release (37, 38). Using 2x3 and 2x5 matrix formulas, respectively, six sustained-release vildagliptin formulations and ten immediate-release dapagliflozin formulations were developed to reinforce the therapeutic compliance of patients by providing prolonged blood glucose management. Formulations of dapagliflozin used super disintegrants for quick release, while sustained-release vildagliptin tablets contained release retardants to prolong release, among other excipients.

Sustained-release vildagliptin formulations, specifically formulas A1, A3, and A4, did not meet the hardness requirements, and the A1 formulation failed to meet the friability requirements for tablets intended for providing a sustained release according to USP, 2024 (39). They disintegrated in the following order: A2 > A6 > A1 > A5 > A4 > A3 (Table 2). On the other hand, the dissolution test sequence for vildagliptin formulations was found to be A1 > A2 > A3 > A5 > A6 > A4 within 6 hours (Figure 4). Among the various formulations, A5 was selected as it met all the criteria (27). It exhibited the highest release percentage after 360 min of the study, beneficial for maintaining stable blood glucose levels for an extended

period, compared to the pure drug (40). Due to the lack of suitable sustained-release vildagliptin preparations in the market, a comparison was not conceivable.

Studies on dapagliflozin formulations' kinetics, stability, and pre- and post-compression parameters exposed that they met the criteria for weight, hardness, friability, and disintegration (23). The order of disintegration was: F6 > F5 > F4 > F1 > F2 > F3 > F7 > F8 (23). Preferred immediate-release formulations was identified by dissolution testing over 60 minutes as F1 > F10 > F9 > pure drug (Figure 4) (23). Furthermore, F1 complied with USP specifications for immediate-release medication profiles, making it suitable for quick blood glucose regulation (23).

Among the three bilayer tablet formulations (BT-1, BT-2, and BT-3), BT-1 exhibits the most favorable dissolution profile, making it the optimal choice. The BT-1 immediate-release layer guarantees a quick onset of action by achieving 84.23% drug release in 60 minutes, which is very similar to dapagliflozin F1's dissolution behavior (Table 3). Furthermore, the sustained-release layer of BT-1 exhibits a prolonged and regulated release of the drug, dissolving 80.03% over 360 minutes. This release profile is very similar to that of vildagliptin A5, which guarantees sustained therapeutic efficacy and sustained drug levels.

Compared to BT-2 and BT-3, BT-1 provides a balanced and desirable release pattern, effectively combining immediate therapeutic action with sustained drug availability. The superior dissolution profile of BT-1 suggests it may offer improved bioavailability, better patient compliance, and enhanced therapeutic effectiveness, making it the recommended optimized bilayer tablet formulation.

This study was limited to in-vitro assessments, including dissolution, compatibility, and stability analyses. While the results suggest the formulation is promising for dual drug release, in-vivo pharmacokinetic and pharmacodynamic studies are necessary to confirm its clinical efficacy, safety, and patient adherence benefits.

CONCLUSION

As observed, the composition features of the immediate-release dapagliflozin and sustained-release vildagliptin bilayer tablets align with the study's objectives. These tablets may offer the potential for simplifying the dosing schedule for Type 2 Diabetes Mellitus (T2DM) patients. Further enhancements to these formulations could involve adjusting the quantities or types of excipients utilized. Additionally, conducting in-vivo experiments will elucidate the impact of this formulation on overall human physiology. In essence, these formulations meet the required standards and promise to reduce the medication burden on patients. Furthermore, innovative formulations can be developed by pairing them with novel drugs.

ACKNOWLEDGEMENT

This work was supported by a research grant (2022-23; Reg/Admin-3/63489) from the University Grants Commission, University of Dhaka, Bangladesh. Authors are thankful to Beximco Pharmaceuticals ltd., Bangladesh and Healthcare Pharmaceuticals Ltd., Bangladesh for their assistance in the preparation of the bilayer tablets.

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