Dhaka Univ. J. Sci. 74(1): 127-137, 2026 (January)
Prof. M. Muhibur Rahman Memorial Issue
ISSN 1022 - 2502, E-ISSN 2408- 8528
DOI: https://doi.org/10.3329/dujs.v74i1.83274

In Vitro Evaluation of Bilayer Tablets Comprising Immediate Release Canagliflozin and Sustained Release Vildagliptin

Shyamjit Paul[1], Md Abdus Samadd[2], A Z M Marufur Rahman Bhoiyan[3], Md Raihan Sarkar[3*], Nahid Sharmin[3*], Md. Abdurrahim[4], Md. Farid Ahmed[5], and Md. Alauddin[6]

[1] *Department of Clinical Pharmacy and Pharmacology, Faculty of Pharmacy, University of Dhaka, Dhaka-1000, Bangladesh*
[2] *Department of Pharmacy, Faculty of Science and Engineering, International Islamic University Chittagong, Kumira-4318, Bangladesh*
[3] *Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka, Dhaka-1000, Bangladesh*
[4] *Biomedical and Toxicological Research Institute (BTRI), Bangladesh Council of Scientific and Industrial Research (BCSIR), Dhaka-1205, Bangladesh*
[5] *Institute of Glass and Ceramic Research and Testing (IGCRT), Bangladesh Council of Scientific and Industrial Research (BCSIR), Dhaka-1205, Bangladesh*
[6] *Department of Theoretical and Computational Chemistry, University of Dhaka, Dhaka-1000, Bangladesh*

(Received : 26 July 2025; Accepted : 1 January 2026)

Abstract

Type 2 diabetes mellitus (T2DM) accounts for about 90–95% of total diabetic cases which can be sustainably maintained by combined therapy. The goal of this study was to develop a bilayer tablet (BLT) that combines sustained release (SR) vildagliptin and immediate release (IR) canagliflozin to improve the treatment outcomes. Nine canagliflozin and six vildagliptin formulas formulas were tested. To determine the most appropriate formulations, the tablets' physicochemical characteristics—hardness, friability, disintegration, and dissolution—were assessed. The *in-vitro* drug release study of BLT was conducted using 0.1 N HCl and pH 6.8 phosphate buffer (2 and 4 hours, respectively). For stability and compatibility tests, DSC, FTIR, SEM, and TGA were employed. F4 (74.60% release within 60 minutes) and A5 (89.76% release over six hours) were selected as IR and SR for BLTs. The physical parameters of the BLTs were within the permissible range, with an average weight of 381 mg, weight variability of 4.93%, thickness of 5.40 mm, hardness of 6.2 kg, friability of 0.32%, and a disintegration time of 18.2 minutes. The final bilayer tablet showed 81.34% release of canagliflozin within 1 hour and >80% release of vildagliptin within 6 hours, while no instability cases were recorded. The designed formulations revealed accepted *in-vitro* performance. Further development and in-vivo tests should be performed to ensure the desired outcomes.

Keywords: T2DM; Canagliflozin; Vildagliptin; Immediate release; Sustained release

I. Introduction

Diabetes is a complicated, long-term and common illness in the world that is responsible for numerous metabolic abnormalities, and can harm the blood vessels, heart, and other organs.[1,2] Especially, type II diabetes mellitus (T2DM) was recognized in around 462 million individuals (6.28% of the world demographic) in 2017.[3] However, the International Diabetes Federation estimated that it affects more that 13 million people in Bangladesh.[4] Diabetes can be managed by employing a variety of therapeutic choices, such as DPP-4 (Dipeptidyl Peptidase-4) inhibitors, insulin and its analogs, SGLT-2 (Sodium-Glucose Cotransporter-2) inhibitors, and others.[5,6]

Vildagliptin, a DPP-4 inhibitor, improved glycemic control by raising incretin and action duration of glucagon-like peptide 1 (GLP-1).[7,8,9] on the Contrary, SGLT2 inhibitor, canagliflozin, prevents the reabsorption of glucose from the kidney.[10,11] They can be utilized as mono or combined therapy in T2DM cases due to their low risk of hypoglycemia and advantageous weight-neutral effect.[8-11] They also reduces the risk of cardiovascular failure by increasing water excretion.[11,12]

The conventional T2DM management such as lifestyle adjustments, single or multiple medication (prescribing two or more medicine concomitantly),[13] has several drawbacks, including fluctuation on glycemic levels.[14] To overcome these limitations, the combination therapy (two or more medicine integrated in one single dosage form) can facilitate sustained blood sugar control, aid in preserving β-cell function, and postpone the deterioration of glycemic regulation as its drug release was controlled and rationally designed.[9,15]

Previously, bilayer tablets (BLT) of immediate release (IR) dapagliflozin and sustained release (SR) vildagliptin was developed by employing super-disintegrating and release-retardant agents, respectively.[16] Anti-diabetic BLT was also established previous time, such as the BLT of metformin (extended release) and pioglitazone (IR).[17] Another BLT was metformin and acarbose combination.[18] Binary mixture of the two drugs somehow is not plausible because of different release profiles.[19] So, BLT was suitable because two drugs layer in a single tablet will reduce the interactions and can retain their distinct release profiles.[19]

The current study goal was to create a BLT of the IR canagliflozin and SR vildagliptin to achieve a synergistic therapeutic effect. The observed synergism is facilitated by

*Author for correspondence. raihan.rezvi@du.ac.bd and nahidsharmin@du.ac.bd

the bilayer formulation through optimized release kinetics rather than a direct physicochemical interaction between the two drugs. These drugs are also approved for simultaneous use by the FDA.[20-24] Although, several marketed or commercial formulations are available for both drugs, to the best of our knowledge, no bilayer tablet combining canagliflozin and vildaglipt in has been established to date knowledge no bilayer of canagliflozin and vildagliptin was established till now.

II. Methods and Materials

Material source

Canagliflozin, vildagliptin, sodium starch glycolate (SSG), mannitol, cross povidone, croscarmellose sodium (CCS), magnesium stearate, colloidal anhydrous silica, avicel 101(MCC), hypromellose, and methocel K15M were obtained from Healthcare Pharmaceuticals Ltd. (Bangladesh)

Compatibility and stability experiment of drug and polymers

Fourier transform infrared (FTIR) Spectrometry. The IR Spirit Infrared Spectrophotometer (Shimadzu, Japan) was used for FTIR analysis. About 300 mg of KBr was finely ground, then mixed with 1 mg of pure drug or drug-excipient blend. The mixture was compressed into a tablet using an IR press at 8 tons.[24,25]

Compatibility and stability testing of the raw materials by FTIR Spectroscopy

API and excipient blends were stored in a stability chamber (30 days) at 25±2°C and 30-65% RH to assess interactions and degradation. FTIR analysis was performed on day 1 and day 30 to detect changes and evaluate formulation stability (scanning range 4000-600 cm^{-1}), and results were compared with literature and initial FTIR peaks (before 30 days).[27]

Thermal analysis (TGA and DSC) studies. Thermogravimetric analysis (TGA) and Differential Scanning Calorimetry (DSC) were employed using a thermal analyzer (NETZSCH STA 449 F5) under a nitrogen-rich environment with a heating rate of 10 K/min. The sample was positioned in and enclosed within a typical aluminum pan and examined between 25°C and 300°C.[6,49] Graphs of thermal analysis were generated by NETZSCH Proteus Software.

Study of surface morphology by scanning electron microscopy (SEM). Field Emission SEM (FESEM, JSM 7610F, Joel Ltd., Japan) captured microscopic images[6] of IR, SR, and bilayer surfaces before and after dissolution. Samples with different excipients were analyzed at 15 kV to examine surface morphology.[6] Dried samples were mounted on a stub with conductive tape or epoxy and vacuum-coated with gold in an argon environment before inspection.

Formulation of IR canagliflozin and SR vildagliptin tablets

A full factorial design (3×3 = 9) was used to assess IR canagliflozin tablets by varying super-disintegrants (CCS, SSG, crospovidone) (Table 1). Similarly, a 3×2 = 6 design evaluated SR vildagliptin tablets by adjusting release retardants (Hypromellose, Methocel K15M) (Table 2). API mass remained constant at 50 mg, with tablet weight adjusted using Avicel 101. Tablets were produced via wet granulation. Avicel 101 was mixed with water to form mucilage, then blended with other ingredients (excluding glidant and lubricant). The slurry was passed through a 40-mesh screen, dried at 30–45°C until LOD <5%, and blended with lubricants sieved through a 20-mesh screen for uniform granule size.[16,28]

Table 1. For the immediate release canagliflozin tablets formulation

Materials	Justifications	F1	F2	F3	F4	F5	F6	F7	F8	F9
Canagliflozin	API	50	50	50	50	50	50	50	50	50
Crospovidone	Disintegrating agent	6	8	10						
Sodium Starch Glycolate	Disintegrating agent				10	12	14			
Croscarmellose Sodium	Disintegrating agent							4	8	12
Magnesium Stearate	Lubricant	2	2	2	2	2	2	2	2	2
Colloidal Anhydrous Silica	Glidant	2	2	2	2	2	2	2	2	2
Mannitol	Filler	60	60	60	60	60	60	60	60	60
Avicel 101(MCC)	Binder/Filler	80	78	76	76	74	82	82	78	74
Total		200	200	200	200	200	200	200	200	200

Table 2. For the sustained release vildagliptin tablets formulation.[16]

Materials	Justifications	A1	A2	A3	A4	A5	A6
Vildagliptin	API	50	50	50	50	50	50
Hypromellose	Release Retardant	50	75	100			
Methocel K15M	Release Retardant				50	75	100
Magnesium Stearate	Lubricant	2	2	2	2	2	2
Colloidal Anhydrous Silica	Glidant	2	2	2	2	2	2
Avicel 101 (MCC)	Filler/Binder	96	71	46	96	71	46
Total		200	200	200	200	200	200

Formulation of BLTs

A BLT was formulated by combining canagliflozin IR 200 mg layer and vildagliptin SR 200mg vildagliptin layer. Both blends were precisely weighed and compressed separately. The SR vildagliptin layer was first placed into rotary tablet dies and lightly compressed to form a uniform layer. The IR canagliflozin mix was then added, and compression force was increased using a Minipress (4B+4D) machine. Tablets measured 14.60 × 7.60 mm, had an oblong shape with embossing or debossing, and maintained a weight of 400 ± 20 mg. Hardness ranged from 4 to 10 kg.[16,29]

Physical parameters

Weight Variation. The mean weight of ten tablets was measured, and individual tablet weights were recorded to calculate the standard deviation.

Thickness. A Mitutoyo digital vernier caliper was used to measure the thickness of ten randomly selected tablets.

Hardness. Monsanto hardness tester was employed to determine the tablets' hardness.[30]

Friability. A total of ten tablets were randomly selected and placed in the drum of a tablet friabilator, which remained upright and completed 100 rotations within four minutes. The tablets stayed still until they were properly balanced. The percentage of weight reduction was determined using the following equation.[30]

$$\%F = (1 - \frac{Wt}{W}) \times 100$$

Where, Wt = weight of the tablets after rotation, % F = friability, W= primary weight of tablets

***In vitro* disintegration test.** Disintegration testing (Electrolab ED-2L) was performed in distilled water (37 ± 2°C, 30 strokes/minute). Tablets were tested until fully disintegrated or non-disintegrable fragments remained. IR and SR tablets were evaluated in 0.1 N HCl, (as IR layer will be disintegrate at stomach) and pH 6.8 phosphate buffer, respectively as SR layer absorbed at the intestine. The acceptable disintegration time was 3–5 minutes for IR tablets and up to 30 minutes for SR tablets.[31]

***In vitro* dissolution study.** A standard curve for both canagliflozin and vildagliptin were constructed. As dissolving media, 0.1 N HCl media for IR canagliflozin and pH 6.8 phosphate buffer for SR vildagliptin were employed. For standard curve, 50 mg of both APIs were diluted by adding specified media up to 100 ml. Different concentrations of the canagliflozin including 0, 2, 4, 8, 12, 16, and 20 µg/ml were prepared through serial dilution approach (absorbance at 291 nm).[32] Moreover, vildagliptin solution was appropriately diluted with pH 6.8 phosphate buffer to obtain concentrations of 0, 2, 4, 8, 12, 16, and 20 µg/mL (absorbance at 210 nm).[16,33]

In-vitro dissolution study was conducted for IR canagliflozin by employing USP apparatus II (0.1N HCl as it mimics the stomach pH). Samples for the IR layer were taken at 5, 15, 30, 45, and 60 minutes (absorbance at 291 nm).[34]

The *in-vitro* dissolution study for SR vildagliptin was conducted using USP apparatus II (pH 6.8 phosphate buffer as it mimics the intestine pH). Samples were collected at 5, 10, 15, 30, 45, 60, 90, 120, 180, and 360 minutes, (absorbance at 210 nm).[33]

In-vitro dissolution study of the BLTs was conducted using both 0.1N HCl and pH 6.8 phosphate buffer media by employing USP apparatus II using 100rpm at 37˚C as both canagliflozin and vildagliptin in the BLT absorbed at the intestine. Samples were withdrawn at 5, 15, 30, 45, and 60 minutes at acidic media (0.1N HCl) and analyzed for both IR canagliflozin and SR vildagliptin at 291 nm and 210 nm, respectively. Other samples for vildagliptin only were collected at 5, 10, 15, 30, 45, 60, 90, 120, 180, and 360 minutes employing pH 6.8 phosphate buffer media (absorbance at 210 nm).

III. Results and Discussion

Stability test through FTIR, DSC, TGA, and SEM

The bands of pure canagliflozin are seen at 1002 cm^{-1} (-C=O), 1076 cm^{-1} (etheral linkage), 1506 cm^{-1} (N=O), 1651 cm^{-1} (C=C), and 3321 cm^{-1} (N-H),[36–38] which were also observed at the same wavelengths after 1 month (Figure 1 a&b). The observed peaks of canagliflozin blends before and after 1 month were seen at 1462 cm^{-1}, 2916 cm^{-1}, and 3344 cm^{-1} (Figure 1c & d). For the pure vildagliptin, the typical bands are seen at 1250-1000 cm^{-1}, 1076 cm^{-1}, 1725-1705 cm^{-1}, 1550-1350 cm^{-1}, 2260-2220 cm^{-1}, 3000-2840 cm^{-1}, and 3500-3060 cm^{-1}.[33] Peaks of Pure vildagliptin were at 1657 cm^{-1}, 2242 cm^{-1}, 2914 cm^{-1}, and 3294 cm^{-1} (Figures 1e & f), which were similar after 1 month. The blend peaks of vildagliptin before and after 1 month were at 1657 cm^{-1}, 2914 cm^{-1}, and 3297 cm^{-1} (Figure 1g & h). From these data, it was clear that no potential interactions occurred between the APIs and the additives. Figure 2a shows IR canagliflozin peaks at 100°C (moisture loss) and 160°C (melting point), confirming crystallinity. Figure 2b displays SR vildagliptin peaks at 65°C (moisture loss) and 150°C (melting point).

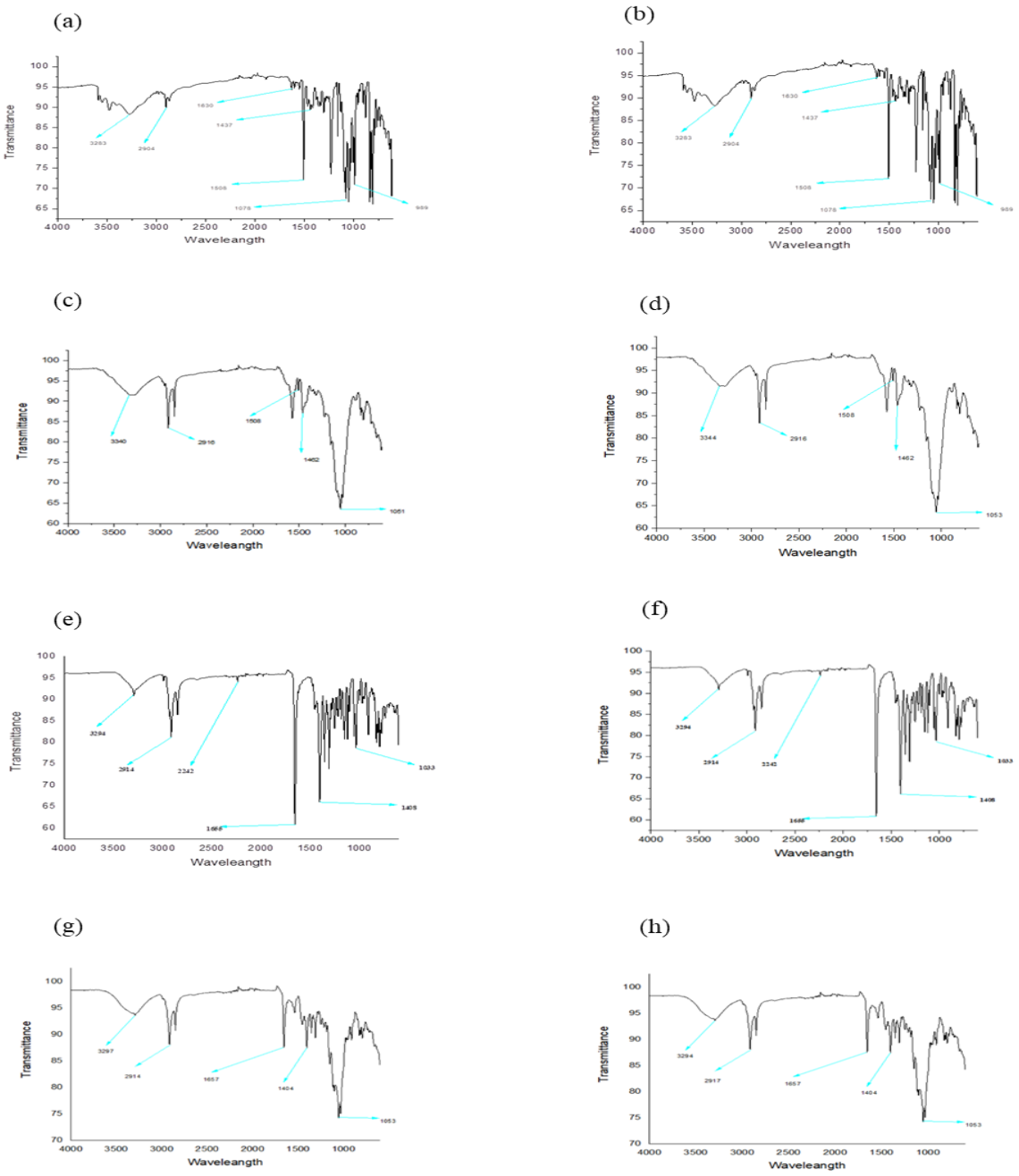


Fig. 1. FTIR spectrum of **(a)** canagliflozin raw material **(b)** canagliflozin raw material after 1-month **(c)** canagliflozin Blend **(d)** canagliflozin blend after 1-month **(e)** vildagliptin raw material **(f)** vildagliptin raw material after 1-month **(g)** vildagliptin blend **(h)** vildagliptin blend after 1 month. [16]

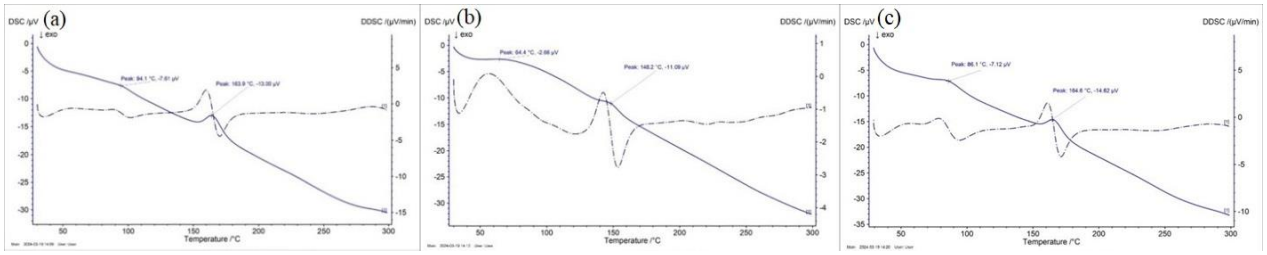


Fig. 2. (a) DSC data immediate release of formulation of canagliflozin. (b) DSC data sustained release formulation of vildagliptin. (c) DSC data of the bilayer formulation of canagliflozin and vildagliptin. [16]

The BLT thermogram (Figure 3c) shows transitions at 86°C and 165°C, indicating excipient interactions. The absence of significant interactions or degradation confirms thermal stability for pharmaceutical use. TGA analysis (Figure 3a-c) displayed excellent thermal stability up to ~200°C. IR canagliflozin has minimal moisture loss, with degradation between 200–300°C (Figure 3a). SR vildagliptin remains stable up to 200°C, with moisture loss at 72.1°C and degradation at 240.5°C (Figure 3b). The bilayer formulation shows minor moisture loss (~1.00%) and controlled degradation beyond 200°C (Figure 3c). These results confirm the formulations' suitability for pharmaceutical processing and storage. The SEM analysis revealed distinct microstructural characteristics. The IR canagliflozin tablet (Figure 4a) has a porous, irregular surface for rapid disintegration and dissolution, though microstructural defects may affect mechanical strength. The SR vildagliptin formulation (Figure 4b) features a structured polymeric coating with controlled porosity, enabling sustained drug release.[16] The BLT (Figure 4c) shows a dual-layer system. The compatibility studies of the formulations by FTIR, DSC, and TGA methods exhibited no discernible interaction between the API, and excipients. Together, this is the first time that a BLT with IR canagliflozin and SR vildagliptin meets all the physicochemical requirements and offers enhanced therapeutic efficacy. Surface morphology of the formulated tablets analyzed through SEM revealed that the IR formulations exhibited a porous surface, which is feasible for faster disintegration into gastric media. Contrary, the SR formulations exhibited a compact, uniform surface structure, which assists in controlling the release of vildagliptin over a longer period.

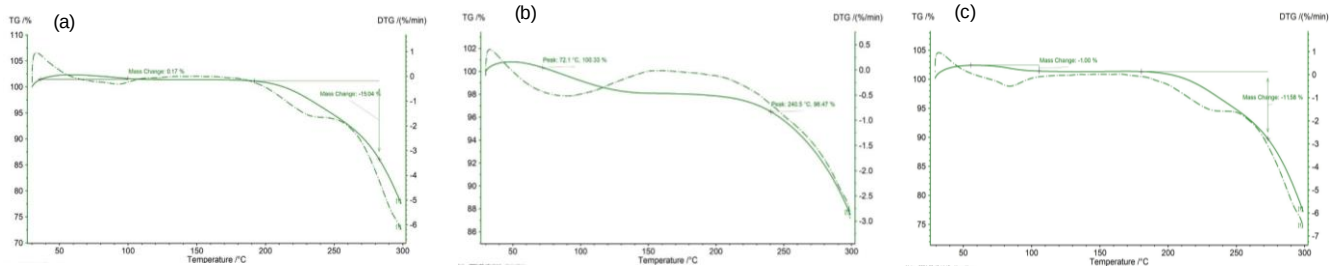


Fig. 3. (a) TGA of *immediate release* canagliflozin formulation (b) TGA of *Sustained release* Vildagliptin formulation (c) TGA of bilayer canagliflozin and vildagliptin formulation.[16]

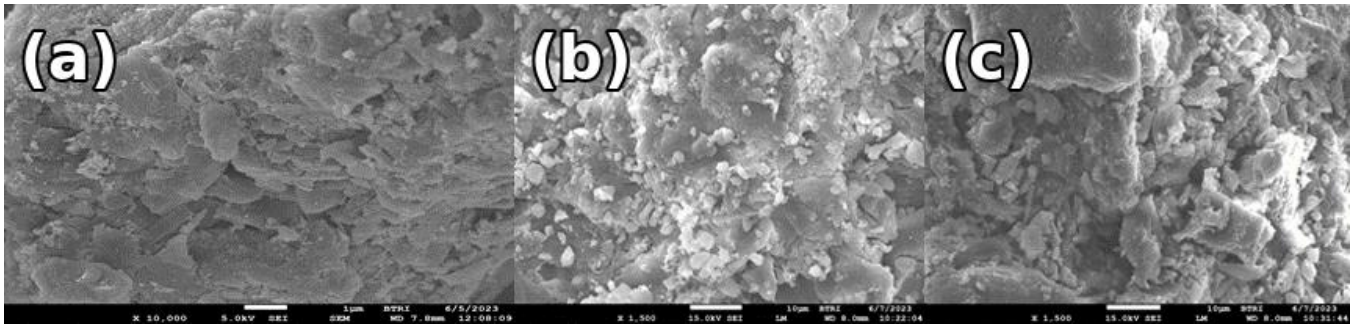


Fig. 4. Scanning electron microscope study of the (a) immediate release (IR) canagliflozin, (b) sustained release (SR) vildagliptin formulation[16] and (c) the bilayer tablets.

IR canagliflozin formulations and SR vildagliptin

All the formulations showed average weight between 194±3.00 mg to 207±3.50 mg. For IR canagliflozin and SR vildagliptin, the prepared tablet demonstrated hardness (4.5-6.9 kg/cm^2 and 4.6 to 6.4 kg/cm^2, respectively). The friability of all the tablets was found to be less than 1%, except for A1 formulation (1.05%) for SR vildagliptin. Formulation F4 displayed the lowest disintegration time, 2.9 minutes and A6 showed the highest disintegration time, 26 minutes (Table 3). All the physical properties of the tablets, such as average weight, hardness, disintegration time, and friability were observed within the permissible limit. The *in vitro* dissolution study revealed the complete dissolution of the IR layer within the first hour in acidic medium, while the SR layer consistently delivered vildagliptin in pH 6.8 phosphate buffer medium (over 6-hours).

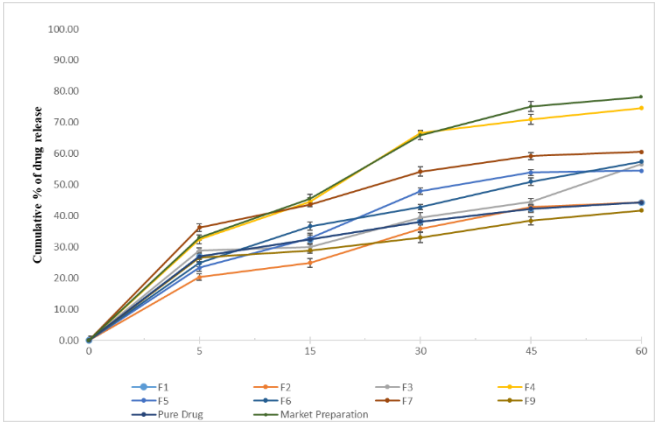
Table 3. Physical characteristics of the Canagliflozin immediate release and vildagliptin sustained release tablets.[16]

Formula	Average weight (mg±SD)	Hardness (kg/cm^2)	Friability (%)	Disintegration time (minutes)
		Physical parameters of the canagliflozin tablets		
F1	195±2.50	4.5	0.59	3.5
F2	196±2.00	5.2	0.57	3.6
F3	201±0.50	6.1	0.49	4.4
F4	198±1.00	6.2	0.49	2.9
F5	201±0.50	6.6	0.47	3.5
F6	203±1.50	6.9	0.43	4
F7	204±2.00	4.8	0.69	3.3
F8	205±2.50	5.2	0.62	3.3
F9	207±3.50	5.6	0.57	3.7
		Physical parameters of the vildagliptin tablets		
A1	194±3.00	4.6	1.05	13.2
A2	195±2.50	5.6	0.92	15.6
A3	198±1.00	6.2	0.83	15.9
A4	201±0.50	5.9	0.72	18.7
A5	203±1.50	6.7	0.57	20.1
A6	203±1.50	6.4	0.62	26

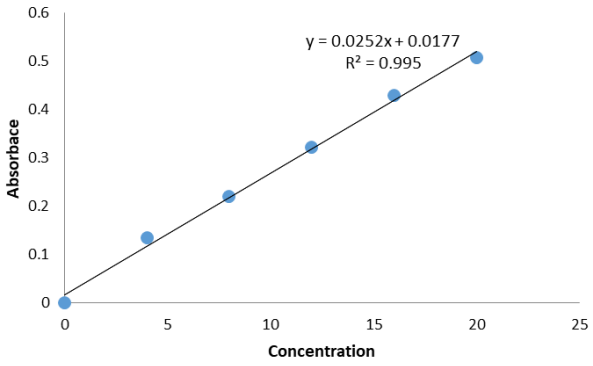
Dissolution analysis of the canagliflozin IR and vildagliptin SR formulations

In the acidic medium (0.1N HCl), pure canagliflozin, showed a 44.30±1.0% drug release within 60 minutes. The F4 formulation, containing SSG as a super-disintegrating agent, demonstrated the utmost drug release profile, 74.60% in 60 minutes, compared to other formulations. The drug release profile of other formulations was, F1 (44.30% ± 1.3), F2 (44.37% ± 0.7), F3 (56.61% ± 1.0), F5 (54.48% ± 0.9), F6 (57.43% ± 1.2), F7 (60.51% ± 1.1), F8 (54.36% ± 0.8), and F9 (41.72% ± 1.3) (Figure 5A, 5B). The comparative dissolution evaluation between the preferred formulation and commercially available canagliflozin, revealed that the F4 formulation had an identical drug release profile.

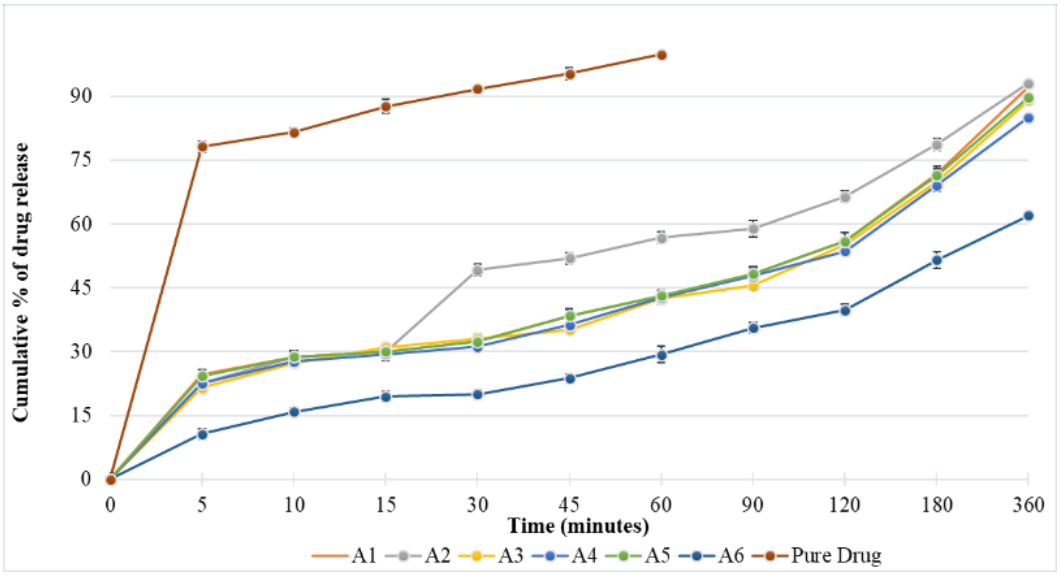
In phosphate buffer medium (pH 6.8), the pure vildagliptin demonstrated 100% drug release within 60 minutes, similar to our previous study.[16,37] Dissolution profiles of the formulations after 6 hours were A1 (92.40%), A2 (93.11%), A3 (89.07%), A4 (85.07%), A5 (89.76%), and A6 (62.04%), respectively (Figure 5B, 5C, 5D). Due to the unavailability of the commercial SR vildagliptin, comparison was not possible.



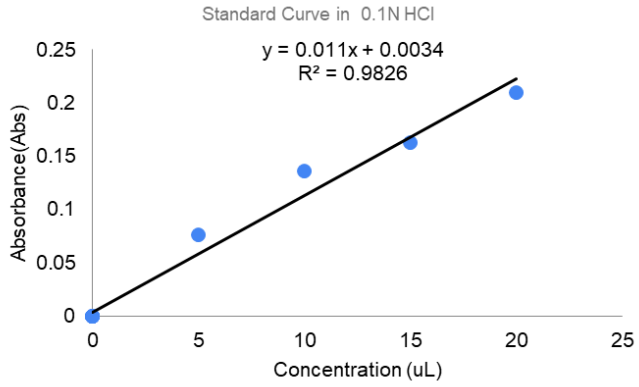
(A)



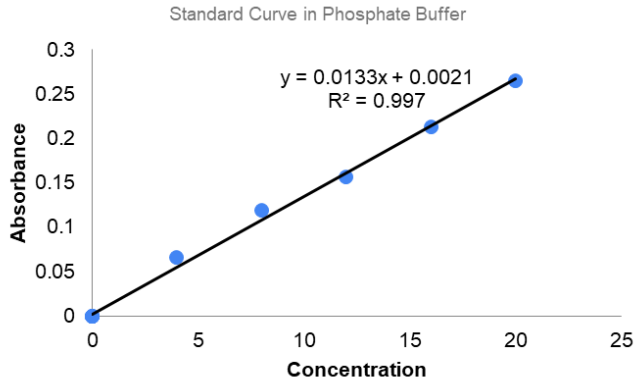
(B)


Cumulative % of drug release
Time (minutes)
A1
A2
A3
A4
A5
A6
Pure Drug

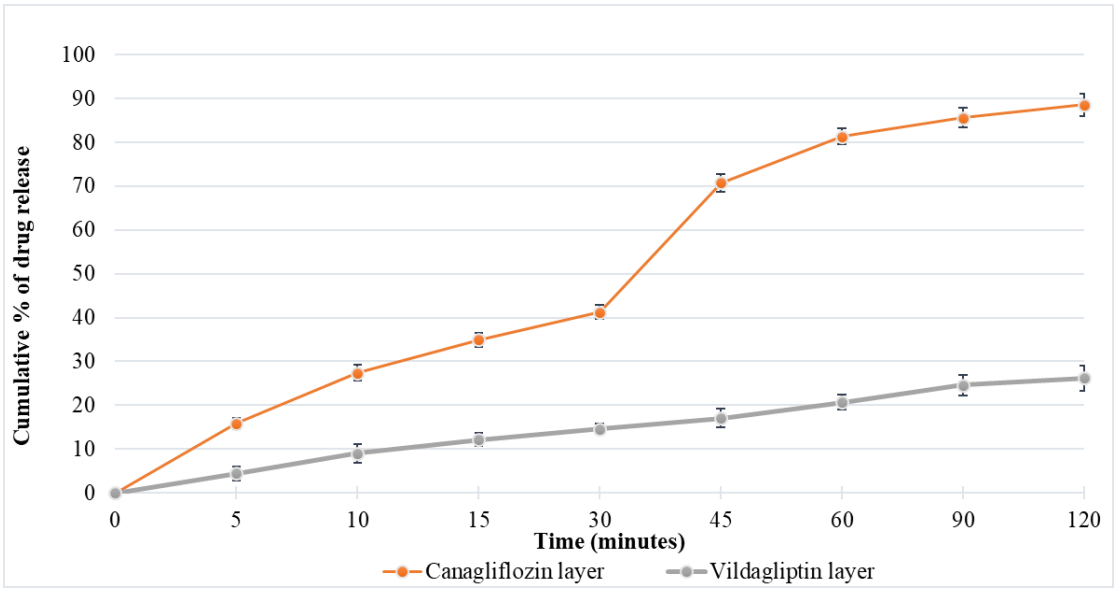
(C)


Standard Curve in 0.1N HCl
y = 0.011x + 0.0034
R² = 0.9826
Absorbance(Abs)
Concentration (uL)

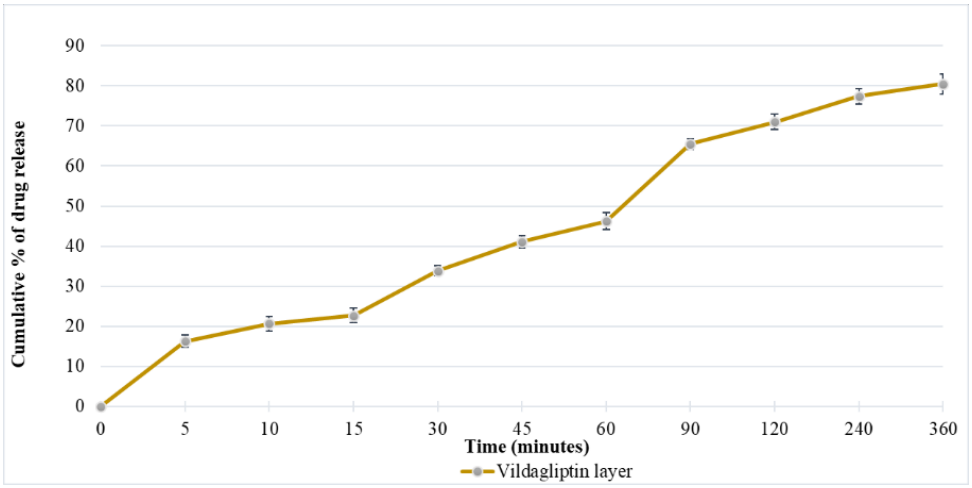
(D)


Standard Curve in Phosphate Buffer
y = 0.0133x + 0.0021
R² = 0.997
Absorbance
Concentration

(E)


Cumulative % of drug release
Time (minutes)
Canagliflozin layer
Vildagliptin layer

(F)



(G)

Fig. 5. The graphs illustrated the cumulative percentage of drug release (Zero Order kinetics) and calibration curve of **(A), (B)** immediate release canagliflozin tablet, **(C), (D), (E)** sustained release vildagliptin table; **(F)**, **(G)** the percentage of release of the bilayer tablet in 0.1 N HCl and 6.8 pH phosphate buffer, respectively.[16]

Characterization and dissolution study of the BLTs

Based on the observed physicochemical characteristics, the BLT was formulated and prepared using the F4 and A5 formulations. The average weight, thickness, hardness, friability and disintegration time of bilayer formulation were 381mg, 5.40 mm, 6.2 kg/cm^2, 0.32% and 18.2 minutes, respectively (Table 4). In acidic media, the IR layer released 81.34% of its drug within 1h, while only 26.20% of vildagliptin was released from the SR layer within 2h (Figure 5F). Vildagliptin continued to release in pH 6.8 phosphate buffer over the next 4h because of release retardants properties (Figure 5G). At the end of 6 hours, a cumulative 80.52% of vildagliptin was released from the bilayer (Figure 5G). Traditionally, the management of T2DM follows lifestyle changes, and employing mono or combined therapy.[13] These methods help to achieve glycemic control but have drawbacks that leading to a transition from mono to BLT.[14] Due to these constraints, early initiation of BLT promotes sustained hyperglycemia control and enhanced β-cell function preservation.[15,39] Canagliflozin is formulated as IR layer due to its long half-life (10.6 hours for 100 mg).[40,41] In contrast, vildagliptin is designed as SR layer, as it has a shorter half-life (3 hours and 69% of vildagliptin is eliminated).[40,42,43] Direct compression was preferred for its cost-effectiveness and efficiency in tablet formulation. The dissolution order of immediate-release (IR) canagliflozin followed F4 > F7 > F6 > F3 > F5 > F8 > F2 > F1 > pure drug > F9 within 60 minutes. Interestingly, disintegration and dissolution times did not correlate with the concentration of disintegrants. For example, F4, with the lowest disintegration time (2.9 minutes), contained only 10 mg of SSG, whereas F3 had a higher disintegration time (4.4 minutes) despite containing 14 mg. No clear relationship was observed between friability, hardness, and disintegration time. The superior drug release of F4 was attributed to the rapid swelling and disintegration properties of SSG, making it the optimized IR formulation. The BLT was formulated using the optimized IR canagliflozin (F4) and SR vildagliptin (A5) formulations. Previous studies reported 89.59% *in vitro* release of IR canagliflozin within 10 minutes and 82.19% release from bilosomes in 1 hour.[46] The current IR formulation (F4) showed a comparable drug release of 81.34% in 1 hour, facilitated by SSG. Rapid dissolution supports quick attainment of therapeutic plasma levels. The SR vildagliptin layer exhibited controlled release, with minimal drug release in acidic media (2 hours) and a gradual release over 6 hours in pH 6.8 phosphate buffer. This sustained release was attributed to matrix-forming polymers, ensuring prolonged therapeutic effects. An extended-release vildagliptin (HPMC K15M containing) showed 98.43% drug release in 10 h of dissolution test.[47] Another *in vitro* drug release study was formulated with pectin and HPMC (75 mg + 75 mg) showed the same efficacy at the SR test (95.1% at 12 hours).[47] Furthermore, prior investigation of a formulation that contained HPMC exhibited release of 98.84% within 24 hrs.[48] In this study, although HPMC was used to prepare the SR layers, their drug release rate was greater than methocel K15M.

Table 4. Physical parameters of the bilayer tablets

Criteria	Observation
Appearance	Smooth, oblong shaped bilayer tablet with grayish canagliflozin part and white vildagliptin part with no break lines
Average weight	381 mg
Thickness	5.40 mm
Weight Variability	4.93%
Hardness	6.2 kg
Friability	0.32%
Disintegration	18.2 minutes

In a previous study on BLTs with IR dapagliflozin and SR vildagliptin, the optimized formulations achieved 80.50% and 81.76% drug release within 30 minutes and 6 hours, respectively. In this study, six SR vildagliptin formulations using Hypromellose and Methocel K15M as release retardants were evaluated. The dissolution order was A2 > A1 > A5 > A3 > A4 > A6 within 6 hours. While A1 and A2 showed the highest drug release rates, they failed to meet required physical parameters due to high friability and low hardness. A5 emerged as the optimized formulation, achieving 89.76% drug release while maintaining acceptable physical properties. Compared to the previous study, A5 is the best candidate for the SR layer.

The study lacks *in vivo* performance which is needed to establish an *in-vitro-in-vivo* correlation. Differences in tablet design, excipients, or other factors could affect results, limiting their applicability to other formulations. Future studies will address these variables. In addition, while the study examined IR and SR drug release, it did not assess extended release over 8–12 hours, which is crucial for evaluating long-term drug effectiveness. Furthermore, 3-6 months stability testing under accelerated conditions are required for robust assessment of stability.

IV. Conclusions

This study developed a BLT containing IR canagliflozin and SR vildagliptin. The optimized formulation met standard physicochemical criteria (SEM, FTIR, DSC, TGA, hardness, thickness, and friability). *In-vitro* testing showed 81.34% drug release within one hour for the IR layer, while the SR layer released 80.52% of vildagliptin over six hours in pH 6.8 phosphate buffer. This formulation could help reduce the dosage regimen for T2DM patients by providing both immediate and extended drug release. Further *in-vivo* studies are needed to confirm bioequivalence and long-term efficacy.

Conflict of Interest

All authors declared no conflict of interest.

Ethical Approval

Not required

Acknowledgments

Authors are grateful to the University Grant Commission, Bangladesh and University of Dhaka (2022-23; Reg/admin-3/63489), and Healthcare Pharmaceuticals for the support of this research, and materials supply, respectively.

References

1. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care **2009; 32(Suppl 1)**:S62–S67.
2. Magliano DJ, EJ Boyko, Committee IDA 10th edition scientific. Global picture [Internet]. In: IDF DIABETES ATLAS [Internet]. 10th edition, International Diabetes Federation, Available from: https://www.ncbi.nlm.nih.gov/books/NBK581940/.
3. Khan MAB, MJ Hashim, JK King, RD Govender, H Mustafa, JA Kaabi. Epidemiology of Type 2 Diabetes – Global Burden of Disease and Forecasted Trends. *Journal of Epidemiology and Global Health* **2019(10)**:107–111.
4. Bangladesh [Internet]. Int Diabetes Fed. Available from: https://idf.org/our-network/regions-and-members/south-east-asia/members/bangladesh/.
5. Scheen AJ. DPP-4 inhibitor plus SGLT-2 inhibitor as combination therapy for type 2 diabetes: from rationale to clinical aspects. *Expert Opinion on Drug Metabolism & Toxicology* **2016(12)**, 1407–1417.
6. Paul, S., T.M., M.A., Uddin, M.A., Samadd, M.S., Rahim, M.R., Hossain, Sarkar, et al. *In-vitro* assessment of immediate release dapagliflozin tablets for type 2 diabetes mellitus treatment. *Bangladesh Journal Of Scientific And Industrial Research* **2024(59)**,139–148.
7. Ceriello A, L C Sportiello, F Rafaniello, Rossi. DPP-4 inhibitors: pharmacological differences and their clinical implications. *Expert Opinion on Drug Safety* **2014(13)** (Suppl 1), 57–68.
8. Das, S., A.K., B., Gupta, B.H., Bandyopadhyaya, V., Darla, M., Arya, Abhyankar, et al. Data on vildagliptin and vildagliptin plus metformin combination in type-2 diabetes mellitus management. *Bioinformation* **2021(17)**, 413–423.
9. Mohan, V., A., M., Zargar, A., Chawla, U., Joshi, B., Ayyagari, Sethi, et al. Efficacy of a combination of metformin and vildagliptin in comparison to metformin alone in type 2 diabetes mellitus: a multicentre, retrospective, real-world evidence study. *Diabetes, Metabolic Syndrome and Obesity* **2021(14)**, 2925–2933.

10. Tanaka, H., K., H., Takano, H., Iijima, N., Kubo, T., Maruyama, Hashimoto, et al. Factors affecting canagliflozin-induced transient urine volume increase in patients with type 2 diabetes mellitus. *Advances in Therapy* **2017(34)** 436–451.

11. Bundhun PK, F Huang. Adverse drug events associated with sitagliptin versus canagliflozin for the treatment of patients with type 2 diabetes mellitus: a systematic comparison through a meta-analysis. *Diabetes Therapy* **2018(9)**, 1883–1895.

12. Rådholm, K., G., V., Figtree, S.D., Perkovic, K.W., Solomon, D., Mahaffey, de Zeeuw, et al. Canagliflozin and heart failure in type 2 diabetes mellitus: results from the CANVAS program. *Circulation* **2018**, 138:458.

13. Fujiwara, Y., S., H., Eguchi, Y., Murayama, M., Takahashi, K., Toda, Imai, et al. Relationship between diet/exercise and pharmacotherapy to enhance the GLP-1 levels in type 2 diabetes. *Endocrinology, Diabetes & Metabolism* **2019(2)**, e00068.

14. Kalra, S., A.K., G., Das, S., Priya, R.N., Ghosh, S., Mehrotra, Das, et al. Fixed-dose combination in management of type 2 diabetes mellitus: expert opinion from an international panel. *Journal of Family Medicine and Primary Care* **2020(9),** 5450.

15. Cahn A, Cefalu WT. Clinical considerations for use of initial combination therapy in type 2 diabetes. *Diabetes Care* **2016(39)**, (Suppl 2):S137–S145.

16. Paul, S., & F., Islam, (2026). 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. *Malaysian Journal of Medicine and Health Sciences*, in-press (Will be published January 2026).

17. Patel D, Patel A, T. Solanki Formulation and evaluation of bilayer tablet by using melt granulation technique for treatment of diabetes mellitus. *Journal of Pharmacy and Bioallied Sciences* **2012(4)** (Suppl 1):S37–S39.

18. Tiwari P, A M Gupta, P Joshi, Tiwari. Bilayer tablet formulation of metformin HCl and acarbose: a novel approach to control diabetes. *PDA Journal of Pharmaceutical Science and Technology* **2014(68)**, 138–152.

19. Rameshwar, V., D Kishor,. and G Tushar,., Bi-layer tablets for various drugs: A review. *Scholars Academic Journal of Pharmacy*, **2014 3(3),** pp.271-279.

20. Dahlén, A.D., G., Dashi, I., Maslov, M.M., Attwood, J., Jonsson, V., Trukhan, et al. Trends in antidiabetic drug discovery: FDA approved drugs, new drugs in clinical trials and global sales. Frontiers Pharmacology **2022(12)**.

21. McInnes, G., M., Evans, S., Del P, M., Stumvoll, A., Schweizer, V., Lukashevich, et al. Cardiovascular and heart failure safety profile of vildagliptin: a meta-analysis of 17,000 patients. *Diabetes, Obesity and Metabolism* **2015(17)**:1085–1092.

22. Monami M, B Ahrén, I Dicembrini, E Mannucci. Dipeptidyl peptidase-4 inhibitors and cardiovascular risk: a meta-analysis of randomized clinical trials. *Diabetes, Obesity and Metabolism* **2013(15)**, 112–120.

23. Patorno E, AB Goldfine, S Schneeweiss, et al. Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study. *BMJ* **2018(360)** :k119.

24. Savarese, G., C., M., D'Amore, F., Federici, De S., Martino, C,. Dellegrottaglie, Marciano, Effects of Dipeptidyl Peptidase 4 Inhibitors and Sodium-Glucose Linked coTransporter-2 Inhibitors on cardiovascular events in patients with type 2 diabetes mellitus: A meta-analysis. *International Journal of Cardiology* **2016(220)**, 595–601.

25. Maddiboyina, B., V., R.K., Jhawat, P.K. Nakkala, Desu, and S., Gandhi, Design expert assisted formulation, characterization and optimization of microemulsion based solid lipid nanoparticles of repaglinide. *Progress in Biomaterials* **2021(10)** :309–320.

26. Maddiboyina, B., V., G., Jhawat, O., Sivaraman, R.K., Sunnapu, M.H., Nakkala, Naik, et al. Formulation Development and Characterization of Controlled Release Core-in-cup Matrix Tablets of Venlafaxine HCl. *Current Drug Therapy* **2020(15)**, 503–511.

27. Baggio LL, DJ Drucker. Glucagon-like peptide-1 receptor co-agonists for treating obesity and diabetes. Mol Metab **2021**; 46:101090.

28. Nauck MA, JJ Meier. Incretin hormones: Their role in health and disease. Diabetes Obes Metab **2018; 20(Suppl 1)**:5–21.

29. Holst JJ. The physiology of glucagon-like peptide 1. Physiol Rev **2007**; 87:1409–1439.

30. Deacon CF. Dipeptidyl peptidase-4 inhibition with sitagliptin: a new therapy for type 2 diabetes. Expert Opin Investig Drugs **2007; 16**:533–545.

31. Bailey CJ, Day C. SGLT2 inhibitors: glucuretic treatment for type 2 diabetes. Br J Diabetes Vasc Dis **2010; 10**:193–199.

32. Ferrannini E, A Solini. SGLT2 inhibition in diabetes mellitus: Rationale and clinical prospects. Nat Rev Endocrinol **2012; 8**:495–502.

33. Zinman, B., C., J.M., Wanner, D., Lachin, E., Fitchett, S., Bluhmki, Hantel, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med **2015**; 373:2117–2128.

34. Neal, B., V., Perkovic, K.W., Mahaffey, D., De Zeeuw, G., Fulcher, N., Erondu, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med **2017**; 377:644–657.

35. Wiviott, S.D., I., M.P., Raz, O., Bonaca, E.T., Mosenzon, A. Kato, Cahn, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med **2019; 380**:347–357.

36. Davies MJ, DA D'Alessio, J Fradkin, WN Kernan, C Mathieu, G Mingrone, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. Diabetes Care **2018; 41:**2669–2701.

37. DeFronzo RA, L Norton, M Abdul-Ghani. Renal, metabolic, and cardiovascular considerations of SGLT2 inhibition. Diabetes Care **2017; 40**: 161–172.

38. J.J., McMurray, S.D., Solomon, S.E., Inzucchi, L., Køber, M.N., Kosiborod, F.A., Martinez, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med **2019; 381**:1995–2008.

39. Packer, M., S.D., Anker, J., Butler, G., Filippatos, S.J., Pocock, P., Carson, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med **2020; 383**:1413–1424.

40. Fitchett, D., B., Zinman, C., Wanner, J.M., Lachin, S., Hantel, A., Salsali, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk. Circulation **2016; 133**:258–264.

41. Kosiborod, M., M.A., Fu, Cavender, A.Z., Wilding, J.P., Khunti, K., Holl, R.W., et al. Lower Risk of Heart Failure and Death in Patients Initiated on SGLT-2 Inhibitors Versus Other Glucose-Lowering Drugs. Circulation **2017; 136**:249–259.

42. Perkovic, V., M.J., Jardine, B., Neal, S., Bompoint, H.J., Heerspink, Charytan. et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med **2019; 380**:2295–2306.

43. Cherney DZI, Perkins BA. Sodium-glucose cotransporter 2 inhibition in type 1 diabetes: Simplicity, complexity, and plasma volume. Diabetes **2020; 69**:782–788.

44. Fadini GP, A Avogaro. Cardiovascular effects of DPP-4 inhibition: Beyond GLP-1. Vascul Pharmacol **2011; 55**:10–16.

45. Zaccardi, F., D.R., Webb, T. Yates, and Davies, M.J. Pathophysiology of type 1 and type 2 diabetes mellitus: A 90-year perspective. Postgrad Med J **2016; 92**:63–69.

46. Thomas, M.C., M., Brownlee, K., Susztak, K., Sharma, K.A., Jandeleit-Dahm, S., Zoungas, P. Rossing, et al. Diabetic kidney disease. Nat Rev Dis Primers **2015; 1**:15018.

47. Cusi K. Role of insulin resistance and lipotoxicity in nonalcoholic steatohepatitis. Clin Liver Dis **2009; 13**:545–563.

48. Drucker DJ. Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1. Cell Metab **2018; 27**:740–756.

49. Mikrani, I., K.M.R., Prattay, M.R., Sarkar, K.Y.K., Sikdar, M. Rahman, and M.A. Samadd, Characterization and In vitro Dissolution Assessment of Pitavastatin-polyvinyl Pyrrolidone and Kollicoat® IR Solid Dispersions Prepared by Solvent Evaporation and Fusion Methodologies. *Bangladesh Pharmaceutical Journal*, **2024(27)** 37-50.