Research Article

Formulation and Evaluation of Bilayer Fixed Dose Combination Tablets Containing Empagliflozin, Sitagliptin and Metformin as Triple Therapy in Diabetes

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ABSTRACT

Empagliflozin, Sitagliptin, and Metformin are oral medications used to manage type 2 diabetes. As the disease progresses, monotherapy often becomes inadequate to maintain glycemic control. Thus, clinically triple therapy is recommended. The aim of this study is to formulate bilayer fixed-dose combination (FDC) tablets containing Empagliflozin, Sitagliptin, and Metformin as a single-dosage regimen. Bilayer tablets were formulated by direct compression method, incorporating Empagliflozin and Sitagliptin in the immediate-release (IR) layer were prepared by Croscarmellose sodium and Sodium starch glycolate. The sustained-release (SR) layer contained Metformin was formulated by HPMC K-100 and Konjac gum. Drug excipient compatibility was assessed using (FT-IR). The powder blends were evaluated for pre-compression parameters, Angle of repose, Bulk density, Tapped density, Hausner's ratio, Compressibility. Formulations were assessed for Thickness, Hardness, weight variation, Friability, Disintegrations, *In vitro* dissolution, Drug content, Invitro enzymatic activity. Based on the dissolution profiles, F6 and E6 were selected as the optimized IR and SR formulations, respectively. F6 showed 95.25% for empagliflozin and 94.50% for sitagliptin within 30 minutes, while E6 exhibited 96.87% for metformin over 12 hours. These were compressed into bilayer tablets. The optimized SR formulation E6 followed first-order kinetics and fit the Korsmeyer Peppas model. The optimized formulation provided effective drug release and presents a promising strategy for triple therapy in type 2 diabetes by enhancing glycemic control and reducing dosing frequency.

Keywords: T2DM, Empagliflozin, Sitagliptin, Metformin, Fixed Dose Combination, Triple Therapy.

INTRODUCTION

American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD), and Clinical guidelines now recommend triple therapy for patients who fail to achieve glycemic targets with dual therapy. Among various routes of administrations oral route remains the most preferred due to its convenience, cost-effectiveness, and patient compliance, particularly in the long-term management of chronic diseases such as type 2 diabetes mellitus (T2DM). A bilayer tablet is an advanced oral dosage form that enables the incorporation of multiple drugs with different release profiles into a single unit, allowing for immediate and sustained release functionalities in one formulation. This approach is especially beneficial in fixed-dose combination (FDC) therapies targeting multiple mechanisms of action, such as the triple therapy.[1-4]

Metformin is BCS Class III (high solubility, low permeability) with 40–50% bioavailability. Empagliflozin and sitagliptin have higher bioavailability (78% and 87%) and belong to BCS Class III. Croscarmellose sodium and Sodium starch glycolate are super disintegrants used in the immediate release layer to rapidly absorb water and swell, promoting fast tablet disintegration and quick drug release. HPMC k-100 (hydroxypropyl methylcellulose) is a hydrophilic polymer used as a matrix former for sustained release, while konjac gum is a natural polysaccharide that acts as a swelling agent and binder in controlled-release formulations.

MATERIALS AND METHODS

Materials

The material used in the immediate release layer (IR) Empagliflozin, Sitagliptin, procured from YARROW CHEM PRODUCTS Mumbai, croscarmellose sodium, sodium starch glycolate, PVPK k-30, magnesium stearate, talc, microcrystalline cellulose and in extended-release layer (ER) Metformin HCL, HPMC K-30, konjac gum, magnesium stearate, microcrystalline cellulose, PVPK k-30.[5-7]

Method[8]

Determination of λmax of Empagliflozin, Sitagliptin, and Metformin in pH 6.8 phosphate buffer:

10 µg/mL solution of CC was prepared using pH 6.8 phosphate buffer and scanned over a wavelength range of 200-400nm using UV-Visible spectrophotometer (®T60 UV spectrophotometer).

Construction of calibration curve of Empagliflozin, Sitagliptin and Metformin in 6.8 pH phosphate buffer:

Standard solutions of Empagliflozin and Metformin (2–10 µg/mL), and Sitagliptin (20–100 µg/mL) were prepared and scanned using a UV-Visible spectrophotometer at their respective wavelengths 223 nm for Empagliflozin, 237 nm for Metformin, and 268 nm for Sitagliptin and process were carried out in triplicate. The absorbed values used to construct a standard graph with concentration on the X-axis and absorbance on Y-axis.

PREFORMULATIUON STUDIES[9]

Determination of melting point:

The melting point of selected APIs were determined by capillary tube method.

Fourier Transform Infrared Spectroscopy (FTIR):

The FTIR analysis was carried out for the pure drugs and bilayer formulation using Aligent Cary 630 FTIR. The sample was placed onto the ATR crystal and pressed down using a swivel press for optimal contact between the sample and the crystal. Each sample was scanned at 4 cm resolution in the range of 4000-650 cm^{-1} wave number.

Formulation of IR-layer and SR-layer:[10]

Accurately weighed Empagliflozin, Sitagliptin, and the required excipients. All ingredients were passed through sieve #60 to ensure uniform particle size distribution. The powders were blended using a mortar and pestle for 10 minutes to obtain a homogeneous mixture. The powder blend was compressed using a 12 mm round flat-faced punch on a tablet compression machine to form the immediate-release (IR) layer by the direct compression method and respectively for SR-layer. The detailed formulations of the IR and SR layers are presented in Table No. (1 & 2).

Table 1: Formulation of immediate release layer (IR)

Ingredients (Mg)	Formulation code					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Empagliflozin	10	10	10	10	10	10
Sitagliptin	50	50	50	50	50	50
PVPK k-30	12	12	12	12	12	12
Croscarmellose sodium	--	--	--	9	12	15
Sodium starch glycolate	9	12	15	--	--	--
Magnesium stearate	6	6	6	6	6	6
Talcum	2	2	2	2	2	2
Microcrystalline cellulose	212	208	206	212	208	206
Total mass	**300**	**300**	**300**	**300**	**300**	**300**

Table 2: Formulation of sustained release layer (SR)

Ingredients (mg)	Formulation code					
	E1	**E2**	**E3**	**E4**	**E5**	**E6**
Metformin HCL	500	500	500	500	500	500
HPMC K-30	140	158	175	--	--	--
Konjac gum	--	--	--	140	158	175
Microcrystalline cellulose	120	120	120	120	120	120
PVPK K-30	30	12	5	30	12	5
Magnesium stearate	10	10	10	10	10	10
Total mass	**800**	**800**	**800**	**800**	**800**	**800**

DEVELOPMENT OF BILAYER TABLETS [10 & 11]

The bilayer tablet formulation was done in two stages. Powder blends of the SR layer (layer 1) and IR layer (layer 2) were prepared and compressed separately for preliminary evaluation. After optimizing each layer, the final bilayer tablet was prepared using selected formulations and compressed with a 12 mm circular punch. Adding saffron color to one layer, usually the upper, visually separates it from the white bottom layer. This helps with identification, minimizes dosing errors, and indicates different release functions.

Figure 1: Bilayer tablet

EVALUATION OF PRE-COMPRESSION PARAMETERS [9]

Angle of Repose:

10 grams of the powder were gently poured through the side of a fixed funnel until a small heap formed at the tip. A circle was drawn around the base of the heap, and its

diameter was measured to assess the flow properties of the powder.

$$\theta = \tan^{-1}(rh)$$

h=Height of the pile

r = radius of the pile base

Determination of bulk density and tapped density:

An accurately weighed amount of powder was poured into a 100 mL measuring cylinder. The initial volume was recorded, after the cylinder was placed on a bulk density tester and tapped for 100 times. The final volume was recorded, and both the bulk density and tapped density were calculated.

Db= Mass of powder/bulk volume of the powder

Dt = mass of powder/ tapped volume of powder

Carr's index:

Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula

$$CI = (TD - BT)\ TDx100$$

Hausner's ratio:

It is used to determine the flowability of the powder by comparing tapped density to the bulk density by using following equation.

Hausner's ratio = Tapped bulk density/loose Bulk density

Hausner's ratio value

EVALUATION OF POST-COMPRESSION PARAMETERS [9]

Weight Variation Test:

Randomly select 20 tablets from the batch and weigh each individually. Calculate the average weight and determine the percentage deviation of each tablet from this average. Compare the deviations with pharmacopeial limits to ensure uniformity.

Hardness:

The resistance of tablets to breakage during storage, transportation, and handling depends on their hardness. A Monsanto hardness tester was used to evaluate this property, and the results were reported in kg/cm².

Friability test:

Ten tablets were accurately weighed and placed in a Roche friabilator, operated at 25 rpm for 100 revolutions. The tablets were subjected to mechanical stress through repeated rolling and impact. The total weight loss before and after the test was recorded, with the resulting reduction used to determine tablet friability. A maximum weight loss not exceeding 1%.

% Friability = initial weight – final weight / initial weight ×100

Thickness:

Thickness of tablet is important for uniformity of tablets size. Vernier caliper is used measure the thickness of tablet. It should be within ± 3% of the prescribed value. The average thickness was estimated in mm.

Disintegration time:

In-vitro disintegration time of the prepared tablets was determined at (37 ± 2ºC) using 900 ml of pH 6.8 phosphate buffer in a disintegration test apparatus. Six tablets were randomly selected and placed in each basket. The apparatus was started, and the time taken for the complete disintegration of the tablets was recorded as the disintegration time.

Drug Content:

An accurately weighed quantity of the powdered tablet, equivalent to 100 mg of the drug, was transferred to a 100 mL volumetric flask. About 50 mL of buffer solution was added, and the mixture was shaken for 10 minutes. The volume was made up to 100 mL with the same buffer solution. The resulting solution was filtered through a membrane filter. A 5 mL portion of the filtrate was further diluted to 100 mL with buffer solution and analyzed using a UV-Visible spectrophotometer at wavelengths of 223 nm, 268 nm and 237 nm.

***In vitro* dissolution studies:**

In-vitro drug release studies of all the formulations were carried out using tablets dissolution test apparatus (USP type-II) at 50 rpm. Phosphate buffer 900 ml, pH 6.8 was used as the dissolution media with the temperature maintained at (37±0.5ºC). For the immediate-release (IR) layer, 5 mL samples were withdrawn at predetermined time intervals of 5, 10, 15, 20, 25, and 30 minutes. For the sustained-release (SR) layer, samples were collected at 2, 4, 6, 8, 10, and 12 hours with replacement of an equal volume of buffer to maintain sink conditions. All samples were filtered, appropriately diluted, and analyzed by UV-Visible spectrophotometry at relevant wavelengths (223 nm, 268 nm and 237 nm), using phosphate buffer as the blank.

MATHEMATICAL MODELING OF DRUG RELEASE PROFILE[12, 13]

The dissolution data of Metformin from the formulated tablets at various time intervals were analyzed using different kinetic models, including zero-order, first-order, Higuchi, and Korsmeyer-Peppas models, to evaluate and characterize the drug release mechanism.

Zero-Order Model:

It describes a drug release rate that is independent of its concentration. If the drug release follows zero-order kinetics, a straight line is obtained when cumulative drug release is plotted against time.

$$Q_t = Q_0 + k_0 t$$

Q_t = amount of drug released at time t

Q_0 = initial amount of drug (usually zero)

k_0= zero-order release rate constant

t = time

First Order Kinetic:

When the drug release follows first-order kinetics, the release rate is proportional to the concentration of the drug remaining. As the concentration decreases, the release rate also decreases, resulting in a logarithmic release pattern.

$$\log C = \log C_0 - 2.303 k_1 t$$

C = drug concentration at time t

C_0 = initial drug concentration

k_1 = first-order rate constant

t = time

Higuchi's Model:

Higuchi's model describes drug release from a matrix system as a diffusion process based on Fick's law, where the amount of drug released is proportional to the square root of time. If the Higuchi model of drug release is obeyed, then a plot of Mt /M∞ versus t1/2 will be straight line with slope of KH.

$$Mt / M\infty = KHt^{1/2}$$

Mt and M∞ =cumulative amount of drug release at time t and infinite time

KH = Higuchi dissolution constant

Korsmeyer-Peppas Model:

It describes the release mechanism from polymeric system expressed in the following equation.

$$Mt/ M\infty = K\ t\ n\ Log\ (Mt / M\infty) = \log K + n \log t$$

ALPHA-AMYLASE INHIBITORY ACTIVITY (DNSA METHOD)[14, 17]

Alpha-amylase inhibition was evaluated using the DNSA method. A mixture of 200 µL of the drug solution and 200 µL of 1% α-amylase was incubated at 30°C for 15 min. Then, 200 µL of 1% starch was added and allowed to react for 10 min. The reaction was stopped by adding 200 µL of 1% DNSA, followed by heating at 35°C for 10 min. The mixture was diluted with 5–6 mL of distilled water, and absorbance was measured at 540 nm. Acarbose was used as positive control.

$$Inhibition\ (\%) = (A\ control - A\ sample)\ A\ control \times 100$$

RESULTS AND DISCUSSION

Determination of λmax of Empagliflozin, Sitagliptin, and Metformin in pH 6.8 phosphate buffer:

The absorption maxima were determined to identify suitable wavelengths for analyzing the drug samples 223 nm for Empagliflozin, 268 nm for Sitagliptin, and 237 nm for Metformin.

Construction of calibration curve of Empagliflozin, Sitagliptin and Metformin in 6.8 pH phosphate buffer:

The calibration graph was plotted to determine the concentration of the unknown sample in 6.8 phosphate buffer. The calibration graph was plotted to determine the concentration of the unknown sample in 6.8 phosphate buffer the R^2 value was shown in the figure 2.

PREFORMULATION STUDIES

Determination of melting point:

Empagliflozin, Sitagliptin, and Metformin showed melting points of 155 °C, 217 °C, and 225 °C respectively, which are in accordance with reported literature values, indicating their identity and purity.

Fourier Transform Infrared Spectroscopy (FTIR):

The FT-IR spectra of pure Empagliflozin, Sitagliptin, Metformin and bilayer tablet and its combination with polymers Figure 3 (i, ii, iii & iv) showed all characteristic peaks, confirming drug-polymer compatibility. The FT-IR spectra of pure APIs and its combinations with Croscarmellose sodium, Sodium starch glycolate, HPMC K-30, Konjac gum, PVPK K-30, Magnesium stearate, Microcrystalline cellulose Talcum exhibited all characteristic functional group peaks within the expected wave number range.

FTIR analysis confirmed the presence of functional groups corresponding to empagliflozin, metformin, and sitagliptin in both pure forms and the bilayer tablet formulation. Empagliflozin showed characteristic peaks for O–H (3423.6 cm^{-1}), aromatic C–H (3239 cm^{-1}), C–O (1060 cm^{-1}), and aliphatic C–H (2862 cm^{-1}). Metformin exhibited N–H symmetric and asymmetric stretches (3160.78, 3354.12 cm^{-1}), N–H bending (1559.89 cm^{-1}), and a C=N stretch (1651.21 cm^{-1}). Sitagliptin showed peaks for C–H alkane (1424.7 cm^{-1}) and C–F (1269.2 cm^{-1}). The bilayer tablets retained all major peaks including O–H, N–H, C=O, and C–F stretches, confirming the presence and compatibility of the active ingredients without structural changes.

EVALUATION OF PRE-COMPRESSION PARAMETERS

Pre-formulation studies were carried out for both the Immediate Release (IR) and Sustained Release (SR) layers. Powder properties such as angle of repose, Carr's index, Hausner's ratio, bulk density, and tapped density were evaluated. All formulations exhibited good flowability and compressibility, indicating their suitability for direct compression. The pre-compression values for the IR and SR layers are presented in Tables 3 and 4.

EVALUATION POST-COMPRESSION PARAMETERS

All tablets appeared smooth and uniform. The weights of the IR and SR layers were maintained at 300 mg and 800 mg, respectively. All tablet batches passed the weight variation test, with results within the acceptable range of 100 ± 5%.

Friability was below 1%, thickness was less than 5 mm, and drug content ranged from 91% to 100%, all within specified limits. The post compression values were observed in Table 5 & 6.

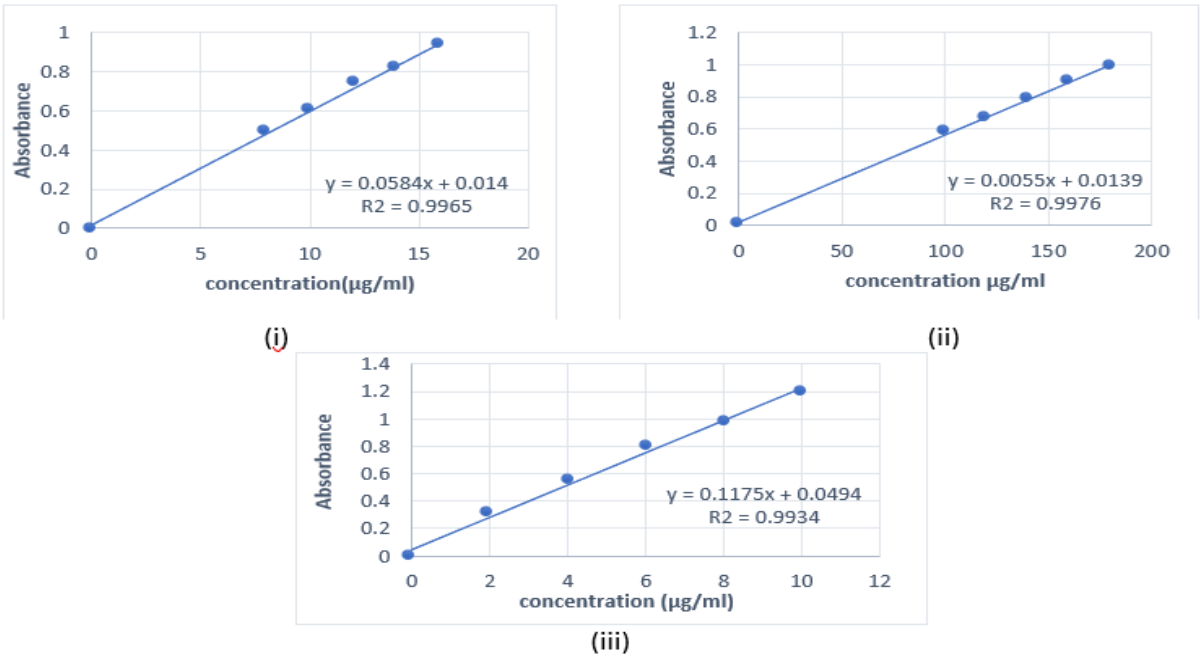

Figure 2: Calibration curve of empagliflozin (i) sitagliptin (ii) and metformin (iii) in 6.8 pH phosphate buffer

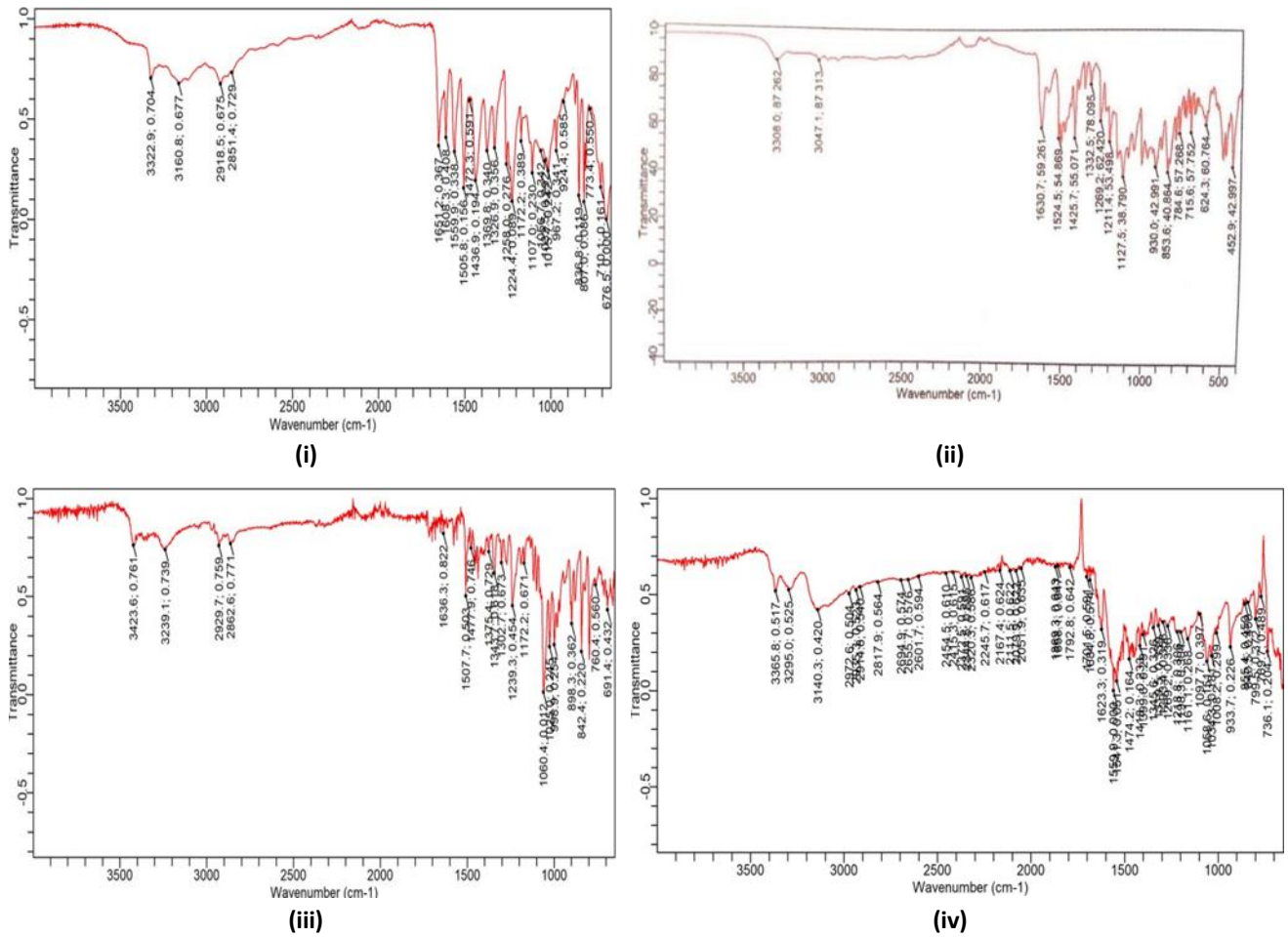

Figure 3: FTIR of Empagliflozin (i) Sitagliptin (ii) Metformin (iii) and Bilayer tablet (iv)

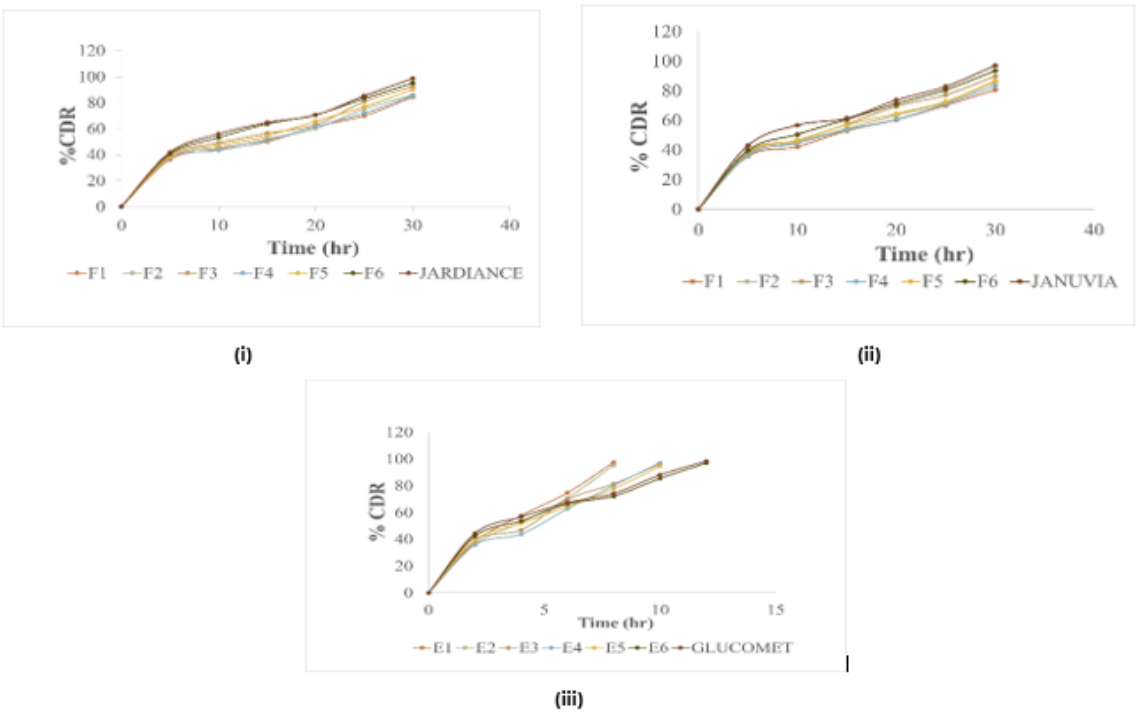

Figure 4: % drug release of Empagliflozin (i) Sitagliptin (ii) and Metformin (iii)

Table 3: Precompression parameters of immediate release layer (IR)

Formulations	Angle of Repose (^{O})	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Index (%)	Hauser's Ratio
F1	28.07±0.032	0.564±0.034	0.68±0.021	17.18±0.040	1.206±0.010
F2	29.05±0.012	0.565±0.038	0.67±0.015	17.49±0.025	1.218±0.017
F3	28.72±0.038	0.570±0.031	0.70±0.017	18.73±0.034	1.229±0.028
F4	27.75±0.039	0.548±0.027	0.67±0.014	18.45±0.017	1.227±0.024
F5	28.39±0.038	0.549±0.016	0.67±0.020	18.42±0.027	1.226±0.037
F6	29.70±0.016	0.555±0.028	0.69±0.025	17.68±0.034	1.213±0.033

Table 4: Precompression parameters of sustained release layer (SR)

Formulations	Angle of repose (^{O})	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Index (%)	Hauser's Ratio
E1	33.69±0.021	0.292±0.025	0.457±0.020	13.40±0.13	1.16±0.015
E2	33.98±0.023	0.294±0.024	0.460±0.021	13.12±0.12	1.18±0.010
E3	33.11±0.020	0.305±0.020	0.507±0.023	14.35±0.14	1.15±0.025
E4	34.59±0.014	0.298±0.022	0.490±0.011	14.01±0.13	1.12±0.020
E5	34.90±0.016	0.290±0.031	0.458±0.021	14.92±0.11	1.15±0.015
E6	33.69±0.021	0.298±0.035	0.482±0.018	13.68±0.17	1.14±0.020

Table 5: Post compression parameters of immediate release layer (IR)

Formulations	Weight variation (mg)	Hardness (Kg/cm²)	Thickness (mm)	Friability (%)	Disintegration time (Sec)	Drug content (%)
F1	0.299±0.02	4.6±0.034	1.0±0.036	0.39±0.021	9±0.023	96.83±0.025
F2	0.297±0.02	4.7±0.048	1.3±0.038	0.36±0.033	10±0.026	94.56±0.036
F3	0.301±0.03	4.7±0.016	1.2±0.029	0.30±0.019	10±0.027	97.66±0.028
F4	0.295±0.02	4.5±0.037	1.1±0.037	0.26±0.045	9±0.032	97.27±0.037
F5	0.302±0.03	4.8±0.039	1.2±0.047	0.36±0.036	10±0.031	96.52±0.039
F6	0.300±0.03	4.9±0.026	1.1±0.037	0.37±0.031	10±0.034	96.89±0.021

Table 6: Post compression parameters of sustained release layer (SR)

Formulations	Weight difference (mg)	Hardness (Kg/cm²)	Thickness (nm)	Friability (%)	Drug content (%)
E1	0.796±0.08	6.4±0.038	4.2±0.028	0.628±0.035	91.46±0.024
E2	0.801±0.07	6.3±0.036	4.2±0.021	0.503±0.038	93.56±0.039
E3	0.796±0.08	6.2±0.030	4.2±0.026	0.375±0.042	92.67±0.019
E4	0.795±0.08	6.3±0.029	4.3±0.034	0.751±0.012	95.91±0.031
E5	0.802±0.07	6.3±0.026	4.3±0.030	0.878±0.018	93.88±0.035
E6	0.799±0.07	6.2±0.021	4.2±0031	0.884±0.015	92.29±0.026

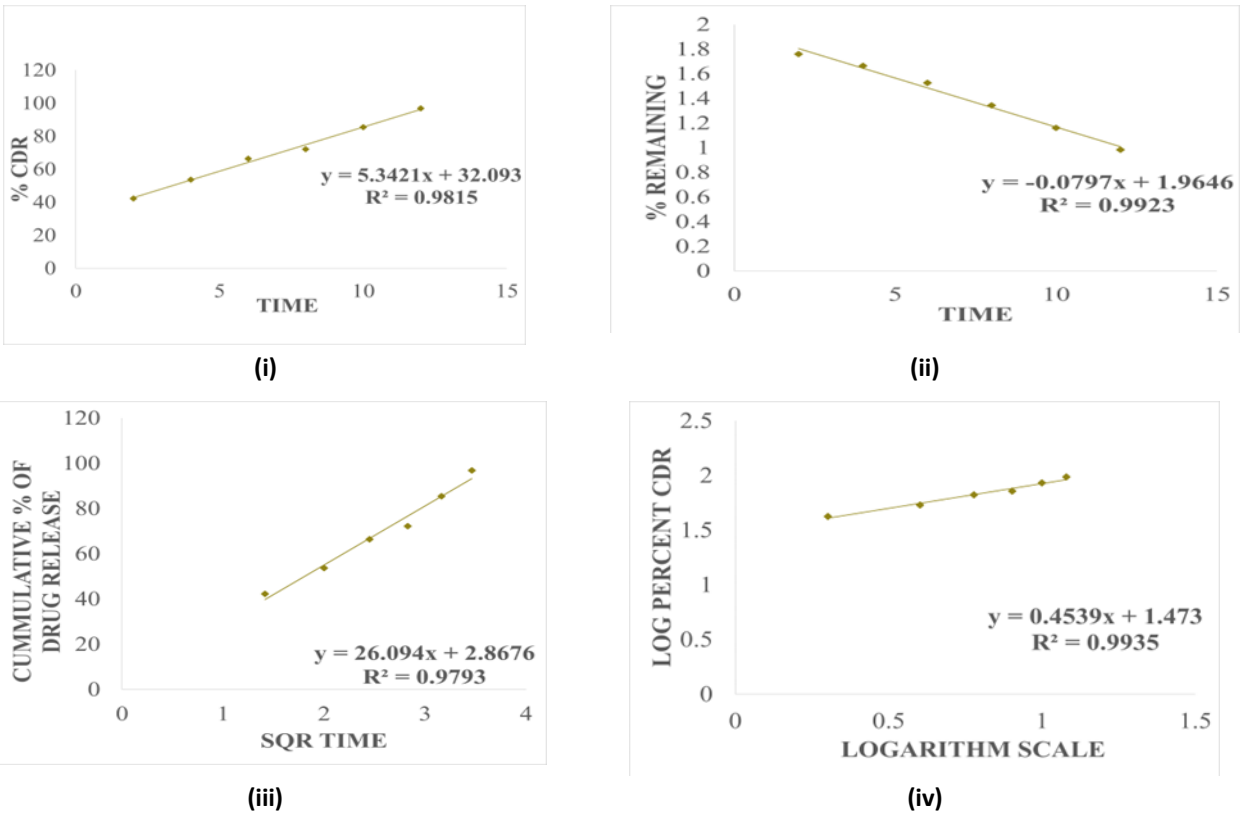

Figure 5: Drug release kinetics of metformin

IN VITRO DISSOLUTION STUDY OF IR-LAYER AND SR-LAYER

In vitro dissolution study of IR layer and SR layer: The cumulative drug release of Empagliflozin, Sitagliptin and Metformin was shown in the figure 4 (I, ii & iii). Among the IR layer formulations (F1 to F6), Empagliflozin demonstrated drug release of 95.25% and Sitagliptin 94.50%, respectively, which are comparable to the marketed formulation. Therefore, F6 was selected as the optimized formulation for the IR layer. In the SR layer formulations (E1 to E6), the E6 formulation showed a drug release of 96.87%, which is also close to that of the marketed formulation. Hence, E6 was selected as the optimized formulation for the SR layer.

DRUG RELEASE KINETICS

The release mechanism of metformin from the optimized formulation was evaluated by fitting the in vitro release data to various kinetic models, including zero-order, first-order, Higuchi, and Korsmeyer-Peppas. The results indicated that metformin release followed first-order kinetics, with an R^2 value of 0.9923, suggesting a concentration-dependent release. Additionally, the formulation also fit well with the Korsmeyer-Peppas model, showing an R^2 value of 0.9902, indicating that the drug release mechanism followed Fickian diffusion. These findings suggest that the sustained release of metformin primarily occurs through polymer swelling and diffusion-controlled mechanisms as show in the figure 5 (i, ii, iii & iv).

ALPHA-AMYLASE INHIBITORY ACTIVITY

The alpha-amylase inhibition assay revealed that Acarbose, the standard inhibitor, exhibited the highest inhibitory activity (91.43%). Among the test formulations, the bilayer tablet showed the greatest inhibition (85.71%), followed by empagliflozin (83.81%), metformin (80.38%), and sitagliptin (77.43%). The high inhibition observed with the bilayer tablet suggests a potential additive or synergistic effect when the three antidiabetic agents are combined. This

indicates that the bilayer formulation may offer enhanced control of postprandial blood glucose through effective inhibition of carbohydrate-digesting enzymes.

CONCLUSION

The bilayer tablet formulation of triple therapy for diabetics, developed by the direct compression method, effectively combines immediate-release Empagliflozin, a sodium-glucose co-transporter-2 (SGLT2) inhibitor that helps reduce blood glucose by promoting glucose excretion through urine, and Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor that enhances insulin secretion and lowers glucagon levels. Metformin lowers blood glucose levels primarily by decreasing hepatic glucose production and improving insulin sensitivity. This triple therapy approach targets multiple complementary mechanisms involved in diabetes management, providing more comprehensive glycemic control than monotherapy or dual therapy. By integrating these three drugs into a single bilayer tablet, the formulation simplifies the dosage regimen and reduces the pill burden for patients, potentially improving adherence and therapeutic outcomes.

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