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FORMULATION AND EVALUTION OF SUSTAINED RELEASE BILAYER TABLET OF GLICAZIDE, PIOGLITAZONE HCL, AND SITAGLIPTIN PHOSPHATE

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ABSTRACT

Diabetes Mellitus 2 is a progressive metabolic disease that has Insulin Resistance and impaired insulin secretion. T2DM usually produces prolonged high blood glucose levels (hyperglycaemia), which makes medication to treat T2DM require combining different types of medication over time. The research described in this paper evaluates the performance of a sustained delivery system for three separate medications to treat T2DM that are combined into a bilayer tablet. One layer (IR) treats fast-rising blood sugars following a meal (postprandial), while the other layer (SR) is designed to maintain multiple therapeutic levels of sitagliptin phosphate and pioglitazone hydrochloride for an extended period of time.[3,4] The comprehensive Preformulation studies that were conducted included the following: Physicochemical characterization of the drug, solubility studies; determination of the melting point; UV spectrophotometric analysis and compatibility studies of the drug and excipients using FTIR spectroscopy. The IR layer was prepared using super disintegrants incorporated into the powder using direct compression, and the SR layer was prepared by wet granulation with hydrophilic polymers such as HPMC K4M and HPMC K100M. Bilayer tablets were evaluated for pre-compression flow properties and post-compression parameters. Additionally, all bilayer tablets were evaluated for consistency of drug content and in vitro dissolution profiles.

According to the study, a bilayer tablet can show mechanical strength that is within acceptable ranges, an immediate release (IR) layer that rapidly disintegrates, and a sustained release (SR) layer that provides drug release over a 24-hour period. The kinetics of drug release was determined to be diffusion controlled. The results of this study indicate that this bilayer tablet will be an effective fixed-dose combination therapy for treating Type 2 Diabetes Mellitus (T2DM) by increasing both the therapeutic efficacy and patient adherence.

KEYWORDS: Bilayer tablet; Sustained release; Immediate release; Gliclazide; Pioglitazone hydrochloride; Sitagliptin phosphate; Type 2 diabetes mellitus.

INTRODUCTION

Over 90% of the global diabetes burden is attributable to "type 2 diabetes" according to the World Health Organisation. Type 2 diabetes occurs because of an excess of glucose in the liver and an increase in fat and insulin resistance within the body, which will lead to a progressive loss of b-cell function in the pancreas. High glucose concentrations for an extended period result from these damaged pancreatic b-cells, and chronic (long-term) high glucose concentrations can lead to serious problems including damage to small vessels (for example, kidney & nerves), damage to large vessels (for example, heart/diseases), and complications related to the feet/eyes (for example, diabetic retinopathy), and even premature death.[1-5]

T2DM is caused by numerous complicated interactions between multiple aspects, making it hard for one drug to provide patient with long-term control over glucose levels. Because of the complexity of T2DM, when patients require drug therapy, it is best to use two or more medications with different modes of action that work together to treat their condition. Gliclazide (second-generation sulphonyl urea) raises insulin levels in the body by stimulating the production of insulin in the pancreas. In addition, pioglitazone (thiazolidinedione) improves the body's sensitivity to insulin by activating PPAR-gamma receptors in many areas of the body. Sitagliptin is a DPP-4 inhibitor that increases incretin hormones in the body that help the pancreas produce insulin in response to elevated glucose levels and inhibit glucagon secretion.[2-7]

Bilayer tablets are an excellent choice for providing a wide range of medications in one convenient dosage form with multiple release rates. Rapidly acting medication provides

immediate relief from symptoms, while continuously releasing medication keeps therapeutic drug concentrations in the blood high for a longer period, which decreases the number of times patients must take a medication throughout the day and thus increases adherence to medication. Therefore, this study will be developing a sustained released bilayer formulation incorporating gliclazide (immediate release) and sitagliptin phosphate and pioglitazone hydrochloride (sustained release).[8-11]

MATERIAL AND METHORD

Material

This study was conducted using drugs (gliclazide, pioglitazone hydrochloride and sitagliptin phosphate) are obtained as gift. The agents used to delay the initial release of each medication in each study consisted of Hydroxypropyl methylcellulose (HPMC) K4M/K100M; Sodium Starch Glycolate (often referred to as Sodium Starch Glycolate) and Croscarmellose Sodium used as Super-Disintegrants; and Polyvinylpyrrolidone (PVP) K30 was employed for binding. Other excipients included Microcrystalline Cellulose for the diluent and Lactose; the Lubricant used was Magnesium Stearate, which is most commonly used in medicines to improve flow properties, and Talc was used as a Glidant. All excipients used were of Analytical Grade.[12-14]

Methods

Preformulation Studies

Organoleptic Properties

All three drugs were examined visually for colour, odour, and appearance.

Melting Point Determination

Melting points were determined using the capillary fusion method.

Solubility Studies

Solubility was determined in various solvents at room temperature.

UV Spectrophotometric Analysis

The λmax values were determined using UV–Visible spectrophotometry.

Drug–Excipient Compatibility Studies (FTIR)

FORMULATION DEVLOPMENT

Formulation of Immediate Release (IR) Layer

The immediate-release layer was designed to provide rapid drug release to achieve prompt onset of therapeutic action. Gliclazide was selected for the IR layer due to its role in controlling postprandial glucose levels.[12-13]

The IR layer was formulated using super disintegrants such as sodium starch glycolate, along with diluents and lubricants. Direct compression was employed due to the good flow properties of the powder blend.[13,15]

Formulation of Sustained Release (SR) Layer

The sustained-release layer was formulated to maintain prolonged plasma drug concentrations. Sitagliptin phosphate and pioglitazone hydrochloride were incorporated into the SR layer.[12-14]

Hydrophilic polymers such as HPMC K4M and HPMC K100M were used as release-retarding agents. Wet granulation was employed to ensure uniform drug distribution and improve compressibility. The polymer concentration was varied to optimize drug release over 24 hours.[12-14]

Formulation of Bilayer Tablets

Bilayer tablets were prepared by sequential compression technique. Initially, the sustained-release layer granules were introduced into the die cavity and lightly compressed. Subsequently, the immediate-release layer blend was added and final compression was performed. This technique ensured clear layer separation and uniform drug distribution in both layers.[13-14]

I. Fig.

Granules A shows the blend of IR layer

II. Fig. Shows the bilayer tablet of glicazide IR, sitagliptin phosphate and pioglitazone hcl SR.

Granules B shows the blend of SR layer.

Table 1: Preparation of IR Glicazide tablet blend.

Ingredients	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)	F7(mg)	F8(mg)	F9(mg)
Glicazide	60	60	60	60	60	60	60	60	60
Lactose	28	25	30	5	9	12	16	19	32
Sodium Starch Glycolate	4	8	12	16	20	24	28	30	34
Cross povidone	8	16	-	20	-	16	-	8	20
Cross carmellose Sodium	-	-	10	-	20	15	-	20	10
Starch	qs	qs	qs	qs	qs	qs	qs	qs	qs
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Total weight	150	150	150	150	150	150	150	150	150

Table 2: Preparation of SR pioglitazone HCL + sitagliptin phosphate tablet blend.

Ingredients	Fs1(mg)	Fs2(mg)	Fs3(mg)	Fs4(mg)	Fs5(mg)	Fs6(mg)	Fs7(mg)	Fs8(mg)	Fs9(mg)
Sitagliptin Phosphate	100	100	100	100	100	100	100	100	100
Pioglitazone HCL	30	30	30	30	30	30	30	30	30
HpMC K4	45	50	55	60	65	75	80	85	95
HpMC K100	60	85	70	90	80	50	45	55	75
Micro crystalline cellulose	165	135	140	120	125	145	150	130	100
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Total weight	400	400	400	400	400	400	400	400	400

EVALUTION

Pre-Compression Evaluation Parameters

Micrometric

Micrometric evaluation of powder blends and granules is a critical step in tablet formulation, particularly for bilayer tablets, as it ensures uniform die filling, reproducible tablet weight, and consistent mechanical strength. In the present study, micrometric properties of both the immediate release (IR) layer blend and sustained release (SR) layer granules were evaluated prior to compression to assess their flow behaviour and compressibility characteristics.

Bulk Density (ρb)

Principle: Bulk density indicates how tightly packed together powders become under very little compaction. It reflects how much space is between particles and how sticky/adhesive the material is between particles. Bulk density is important for predicting how well a powder will flow and how much variability there will be in the weight of tablets produced from powders.

PROCEDURE: One sample of powder blend weighing approximately 20 g was weighed accurately and passed through a #40 mesh sieve before pouring the powder directly into a 100 mL graduated cylinder without compressing the sample in any way. The amount of space occupied by the powder within the cylinder was then recorded as the bulk volume (Vb). The formula for calculating bulk density is as follows:

Bulk Density = [Weight of powder] ÷ [Bulk Volume].

Tapped Density (ρt)

Principle - Tapped density measures powder packing under mechanical tapping and provides insight into powder rearrangement and consolidation behaviour.

Procedure - The same powder-filled graduated cylinder used for bulk density was tapped mechanically for 500 taps using a tapped density apparatus. The final tapped volume (Vt) was recorded.

Tapped density = weight of the powder/ Tapped volume

Compressibility Index (Carr's Index)

Principle - Carr's index is an indirect measure of powder flowability and compressibility. Lower values indicate better flow properties.

Procedure - Bulk and tapped density values were used to calculate Carr's index.

$$\text{Carr's Index (\%)} = [(TBD - LBD) \times 100]/TBD$$

Acceptance Criteria

- ≤ 15% → Good flow
- 15–25% → Fair flow

Hausner's Ratio

Principle - Hausner's ratio evaluates interparticle friction and flowability. Lower ratios signify better flow.

Procedure - Hausner's ratio was calculated using bulk and tapped density values.

Acceptance Criteria

- ≤ 1.25 → Good flow
- 25 → Poor flow

Angle of Repose (θ)

Principle - Angle of repose measures powder flow characteristics under gravitational force. Lower angles indicate better flow properties.

Procedure - The funnel method was employed. Powder was allowed to flow freely through a funnel fixed at a known height. The height (h) and radius (r) of the formed powder cone were measured.

$$\tan\theta = h / r$$

where, θ - is the angle of repose; h- height of the powder cone ;r- radius of the powder cone.

Acceptance Criteria

- < 30° → Good flow
- 30–40° → Passable flow

Evaluation of Bilayer Tablets

Appearance

The tablets were examined for appearance in terms of Colour, Shape, Texture, and Layer Separation. The Tablets had Smooth Surfaces without any visible evidence of Capping, Chipping, or Laminating.

Thickness

The thickness of the Tablets was measured with the help of a digital Vernier Caliper. The consistency of thickness indicated that the Tablets were filled and compressed uniformly during the Manufacturing Process.

Weight Variation

Twenty Tablets were randomly selected from the batch and weighed, and an average weight was calculated and compared with the limits specified by the relevant Pharmacopoeia. All Tablets in all formulations met the standards for Weight Variation.

Hardness

Tablet hardness was measured using a Monsanto hardness tester. Adequate hardness ensured mechanical strength while allowing proper drug release. The hardness of the tablet kg/cm2 is measured.

Friability

Friability was evaluated using a Roche friabilator. Tablets were rotated for 100 revolutions, dedusted, and reweighed. Percentage friability below 1% indicated good mechanical resistance.

Friability is calculated by following formula.

$$\text{Friability} = (W1-W2) \times 100 / W1$$

where, W1 = Weight of the tablets before test; W2 = Weight of the tablets after test

Drug Content Uniformity

Drug Content was determined by dissolving powdered tablets using appropriate media/spectrophotometric analysis of the common components in tablets was used to analyze Teaspoon of each monochloride (monohydrate) used in this study.

The content of the drugs analysed was consistent with the amount expected; therefore, it indicates the uniformity of drug distribution of powdered tablets throughout each study.

In-Vitro Dissolution Studies

Dissolution studies were performed using USP type 11 paddle apparatus and 900 ml phosphate buffer (pH 6.8). Samples were withdrawn at specified time

intervals/spectrophotometrically analysed at the specified times. The initial release from an Immediate Release layer occurred rapidly. The sustained release layer allowed it to release continuously for 24 hours after ingestion.

Release Kinetics

Dissolution data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. The optimized formulation followed diffusion-controlled release, confirming the effectiveness of the hydrophilic polymer matrix.

RESULT AND DISCUSSION

Results of Preformulation Studies

Physicochemical attributes of gliclazide, pioglitazone HCl, and sitagliptin phosphate significantly shaped their formulation strategies according to Preformulation data acquired by performing numerous tests. The three API's demonstrated satisfactory organoleptic characteristics indicating that they were of sufficient pharmaceutical quality and were suitable to be used in oral solid dosages.

- Gliclazide – white or off-white crystalline powder
- Pioglitazone HCl – white crystalline powder
- Sitagliptin Phosphate – white to pale yellow powder

Melting Point Determination

The melting point values of the drugs were found to be within reported literature limits, indicating high purity and absence of degradation.

Drug	Observed Melting Point (°C)	Reported Value (°C)
Gliclazide	169–171	166–168
Pioglitazone HCl	194–196	192–197
Sitagliptin phosphate	211–213	208–215

Solubility Studies,

Solubility studies revealed that gliclazide possesses poor aqueous solubility, while pioglitazone hydrochloride showed moderate solubility and sitagliptin phosphate exhibited good aqueous solubility. These differences justified the selection of a bilayer tablet system, wherein solubility-limited drugs were incorporated into a sustained-release matrix to control dissolution rate.

Solvent	Gliclazide	Pioglitazone HCl	Sitagliptin phosphate
Water	Slightly soluble	Practically insoluble	Freely soluble
pH 6.8 buffer	Slightly soluble	Slightly soluble	Soluble

Methanol	Soluble	Soluble	Soluble
Ethanol	Slightly soluble	Soluble	Soluble

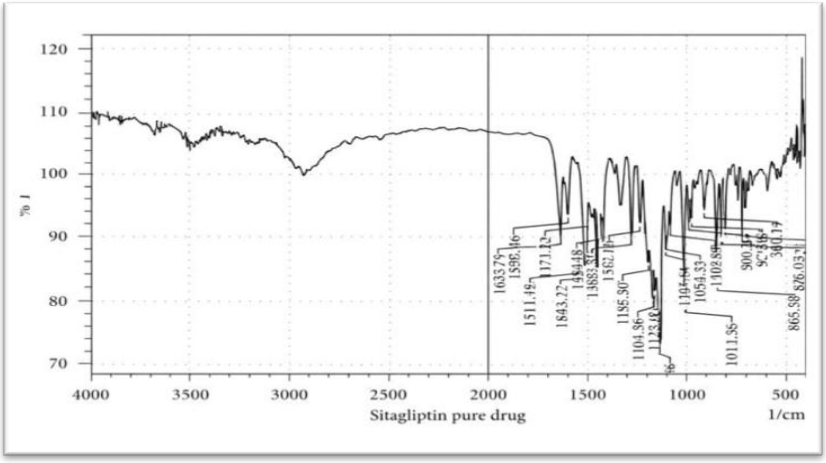
UV Spectrophotometric Analysis

UV–visible spectroscopic analysis confirmed characteristic λmax values for all drugs, and calibration curves demonstrated excellent linearity with correlation coefficients close to unity, validating the analytical method for further evaluation.

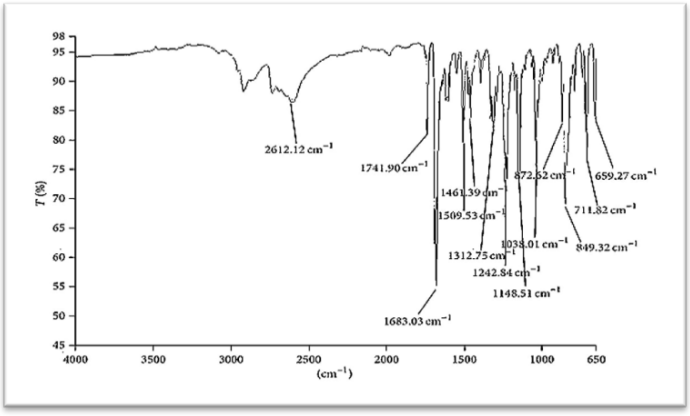
Drug	λmax (nm)
Gliclazide	217
Pioglitazone HCl	269
Sitagliptin phosphate	230

Drug–Excipient Compatibility Studies (FTIR)

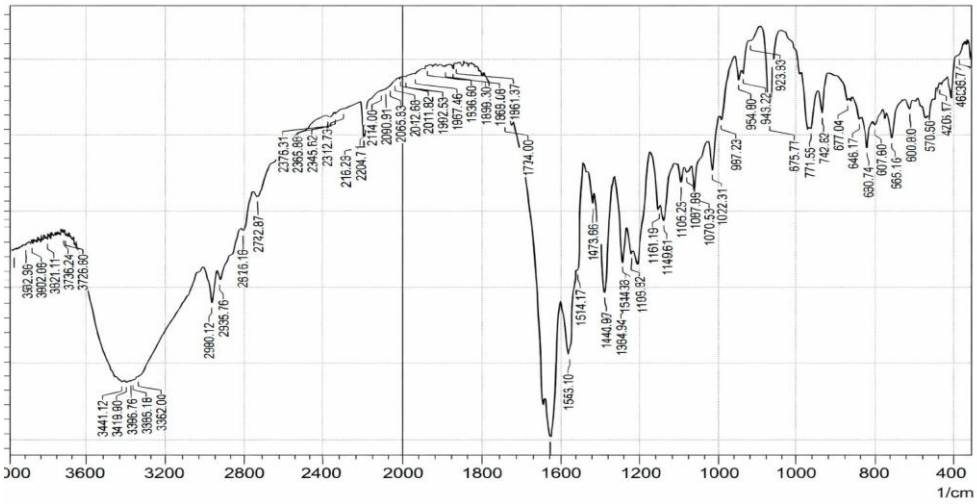
FTIR compatibility studies showed no significant shift or disappearance of characteristic peaks in drug–excipient physical mixtures, confirming chemical compatibility between the drugs.



III. Fig. Ftir spectra of sitagliptin pure drug.



IV. Fig. Ftir spectra of pioglitazone hcl.



V. Fig. Ftir spectra of glicazide.

Evaluation of Immediate Release (IR) Layer

The immediate-release layer containing sitagliptin phosphate was evaluated for micromeritic and physical parameters. Powder blends exhibited acceptable bulk density, tapped density, Carr's index, and Hausner ratio, indicating good flowability suitable for direct compression.

Compressed IR tablets showed uniform thickness, minimal weight variation, and sufficient hardness, confirming consistency of compression. Friability values were below the pharmacopeial limit of 1%, indicating adequate mechanical strength. Drug content uniformity results demonstrated uniform distribution of sitagliptin phosphate within the IR layer.[7,12,15]

In-vitro dissolution studies revealed rapid drug release from the IR layer, with a significant percentage of sitagliptin phosphate released within the initial time period. This rapid release is attributed to the presence of super disintegrants, which facilitated quick tablet disintegration and immediate drug availability, essential for early glycaemic control.[7,12,15]

Table 3: Precompression studies on Glicazide blend.

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bulk Density (gm/ml)	0.32	0.35	0.40	0.45	0.38	0.46	0.42	0.48	0.36
Tapped Density (gm/ml)	0.50	0.48	0.45	0.51	0.44	0.52	0.47	0.53	0.46
Carr's Index	18.6	14.8	24.2	20.4	17.4	16.3	21.5	19.8	22.3
Hausner's Ratio	1.165	1.190	1.215	1.240	1.265	1.290	1.315	1.350	1.385
Angle of Repose	25°.45	27°.22	30°.35	28°.64	26°.38	32°.18	33°.73	35°.11	29°.91

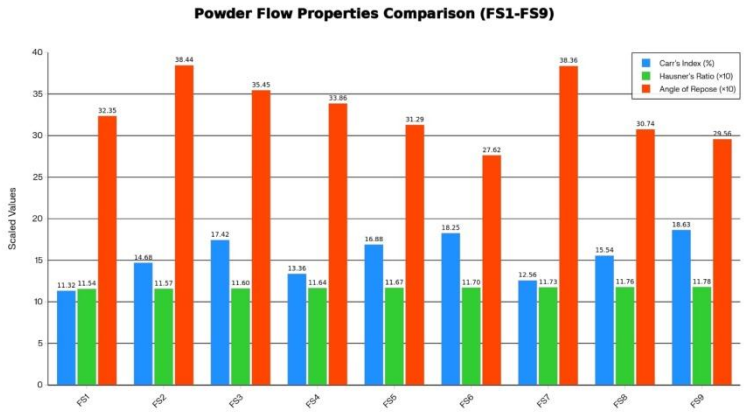
Evaluation of Sustained Release (SR) Layer

In order to control the release rate of Sitagliptin phosphate and Pioglitazone hydrochloride, the drugs were added to an excipient matrix made of hydrophilic polymers (HPs) resulting in sustained release tablets (SRTs). Additionally, wet granulation was able to create granules that have excellent flowability and compressibility, producing a compressed tablet with uniform density during tablet manufacture. The physical characteristics of the SRTs were assessed, with all tablets demonstrating high levels of hardness and identical thickness and weight, and low levels of Friability. Also, drug content analysis confirmed that the two drugs were present in an equal amount within the matrix of each tablet.[12,15]

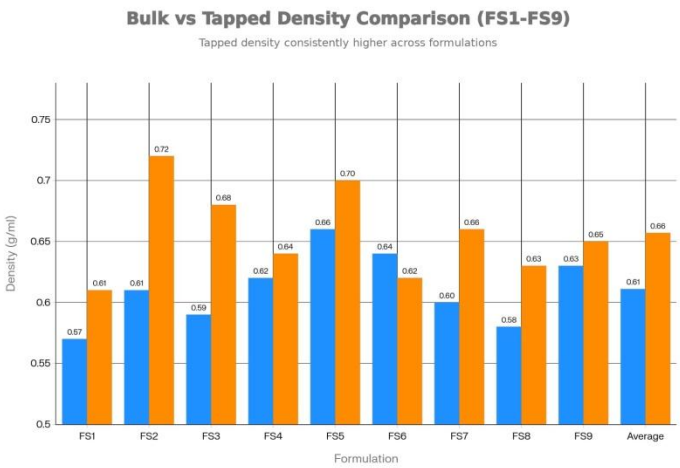
Release studies demonstrated that the amount of HP has a major effect on the release of the drug. Higher concentrations of HPMC K100M polymers in the formulations resulted in a slower rate of release due to the increased gel strength and length of diffusion distance. The hydrophilic polymer matrix also controlled the volume of water entering into the matrix, the quantity of matrix swelling, and how long the drug could diffuse from the matrix over an extended time frame.[7]

Table 4: Precompression studies on pioglitazone hcl + sitagliptin blend.

Parameter	FS1	FS2	FS3	FS4	FS5	FS6	FS7	FS8	FS9
Bulk Density (gm/ml)	0.57	0.61	0.59	0.62	0.66	0.64	0.60	0.58	0.63
Tapped Density(gm/ml)	0.61	0.72	0.68	0.64	0.70	0.62	0.66	0.63	O.65
Carr's Index	11.32	14.68	17.42	13.36	16.88	18.25	12.56	15.54	18.63
Hausner's Ratio	1.154	1.157	1.160	1.164	1.167	1.170	1.173	1.176	1.178
Angle of Repose	32°.35	38°.44	35°.45	33°.86	31°.29	27°62	38°36	30°74	29°56



VI. Powder flow properties comparisons for all nine formulations.

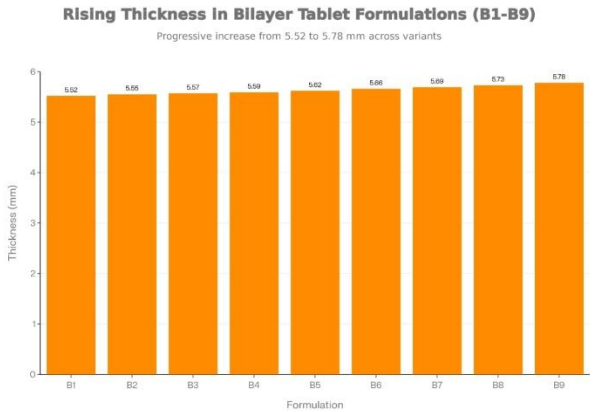


VII. Bulk density vs tapped density for all 9 formulation.

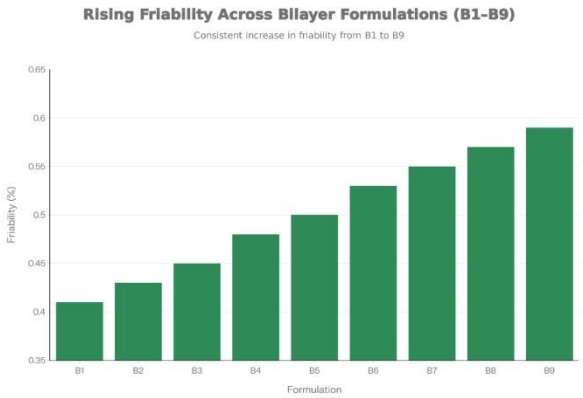
Evaluation of Bilayer Tablets

Bilayer tablets prepared by sequential compression showed clear layer separation with no evidence of delamination or capping. Physical evaluation parameters such as thickness, weight variation, hardness, and friability were within acceptable limits, indicating mechanical stability of the bilayer system.[7,8]

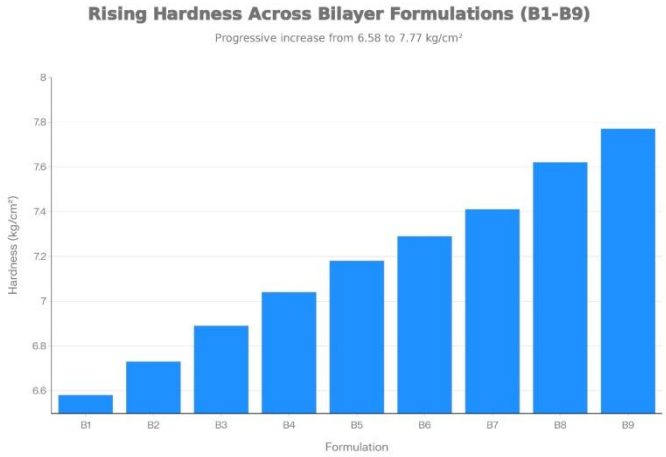
Drug content uniformity studies confirmed accurate dose distribution across both layers, demonstrating the reliability of the compression process. The integrity of the bilayer structure was maintained throughout handling and testing, indicating robustness of formulation.[9,11,15]



VIII. Thickness in bilayer tablet formulations (B1-B9)



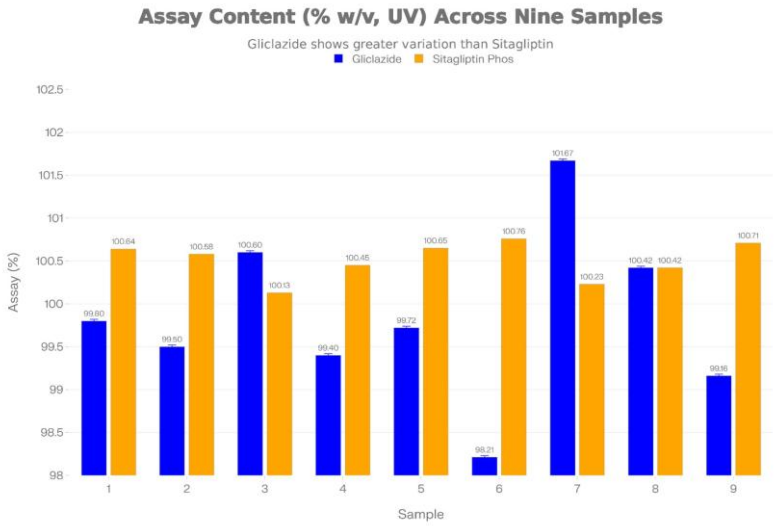
IX. Rising frability across bilayer tablet formulations (B1-B9).



X. **Rising hardness across bilayer formulations (B1-B9).**

Table 5: Post compression studies of bilayer tablet.

Formulation	Parameters				Assay %w/v – UV	
	Weight variation (mg)	Hardness kg/cm2	Friability%	Thickness mm	Gliclazide	Sitagliptin Phosphate
B1	550±0.02	6.58	0.41	5.52	99.8±0.02	100.64
B2	550±0.02	6.73	0.43	5.55	99.5±0.02	100.58
B3	550±0.02	6.89	0.45	5.57	100.6±0.02	100.13
B4	550±0.02	7.04	0.48	5.59	99.4±0.02	100.45
B5	550±0.02	7.18	0.50	5.62	99.72±0.02	100.65
B6	550±0.02	7.29	0.53	5.66	98.21±0.02	100.76
B7	550±0.02	7.41	0.55	5.69	101.67±0.02	100.23
B8	550±0.02	7.62	0.57	5.73	100.42±0.02	100.42
B9	550±0.02	7.77	0.59	5.78	99.16±0.02	100.71



XI. Assay content (%W/U) across nine formulations.

In-Vitro Dissolution Studies of Bilayer Tablets

The results of the in vitro dissolution testing of bilayer tablets indicate a biphasic drug-release profile. The fast-release layer of glicazide allows for quick therapeutic action and the slow-release layers of sitagliptin phosphate and pioglitazone are released in a controlled manner over a period of 24 hours.

The overall dissolution profile showed that the bilayer tablets accomplished both immediate and prolonged release of the drugs in one dosage form. This type of release allows plasma drug concentrations to be maintained at therapeutic levels while decreasing the need for frequent dosing.

Table 6: Comparative In vitro Drug Release Studies glicazide IR.

Time (min)	% Cumulative Drug Release								
	B1	B2	B3	B4	B5	B6	B7	B8	B9
0	0	0	0	0	0	0	0	0	0
5	35.4	27.3	36.1	31.7	29.6	27.3	33.5	30.4	33.6
10	54.5	48.4	49.3	52.7	47.8	51.6	50.3	39.6	42.6
15	73.4	69.3	69.8	68.1	72.8	74.5	72.5	70.4	71.6
20	82.7	80.6	81.7	82.4	83.3	86.1	81.3	80.8	84.6
25	89.1	90.2	93.6	94.8	95.5	96.7	92.5	96.5	98.5
30	98.6	92.7	94.2	95.9	97.5	93.1	95.4	98.3	97.2

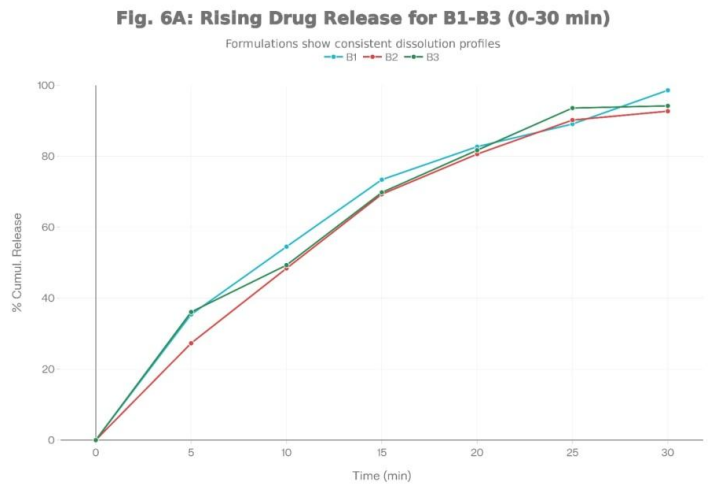


Fig. 6A: Rising Drug Release for B1-B3 (0-30 min)
Formulations show consistent dissolution profiles
B1 B2 B3
% Cumul. Release
Time (min)

A)

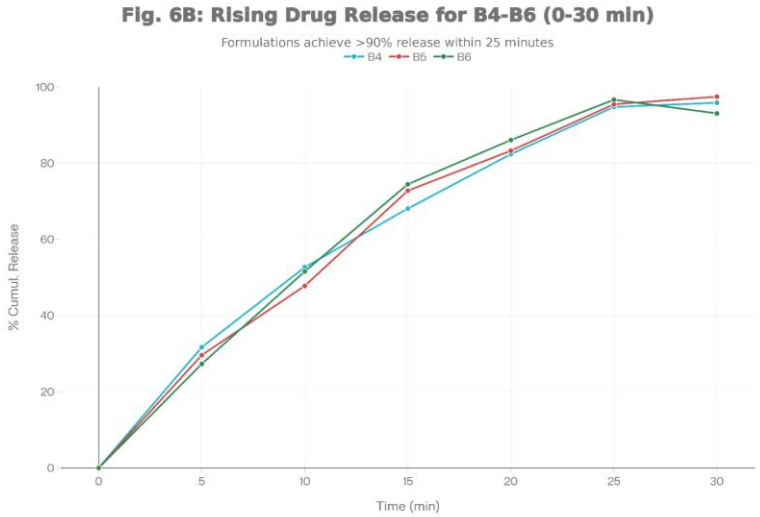
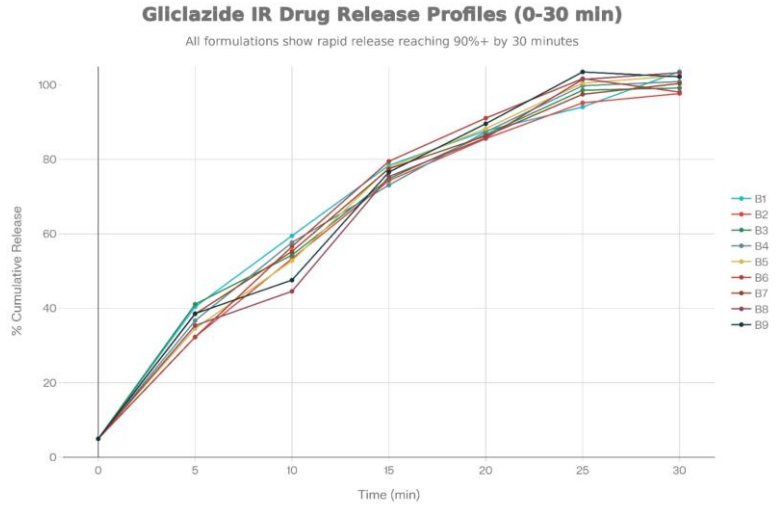


Fig. 6B: Rising Drug Release for B4-B6 (0-30 min)
Formulations achieve >90% release within 25 minutes
B4 B5 B6
% Cumul. Release
Time (min)

B)


Gliclazide IR Drug Release Profiles (0-30 min)
All formulations show rapid release reaching 90%+ by 30 minutes
% Cumulative Release
Time (min)
B1
B2
B3
B4
B5
B6
B7
B8
B9

C)

III. Glicazide IR drug release profiles

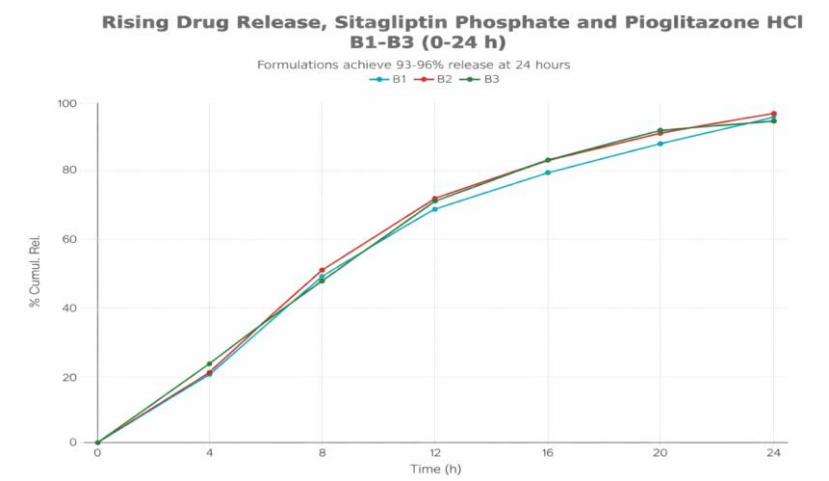
A) Shows for B1 –B3

B) Shows for B4- B6

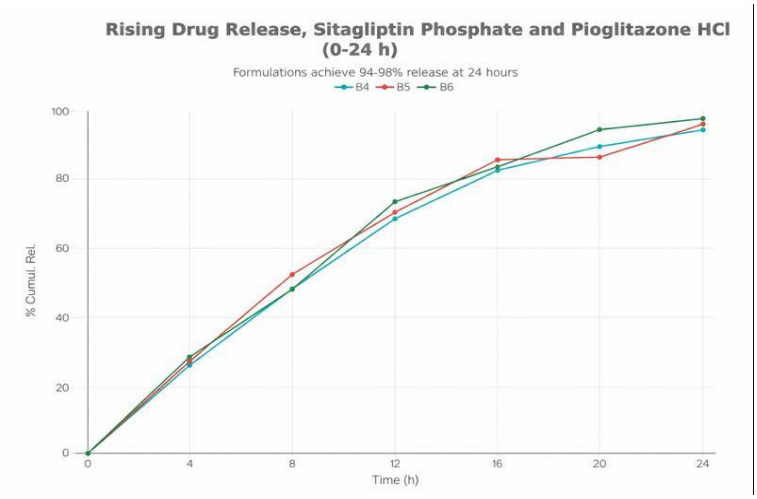
C) For all nine formulations

Table 7: Comparative Invitro Drug Release Studies on pioglitazone HCL and sitagliptin phosphate SR.

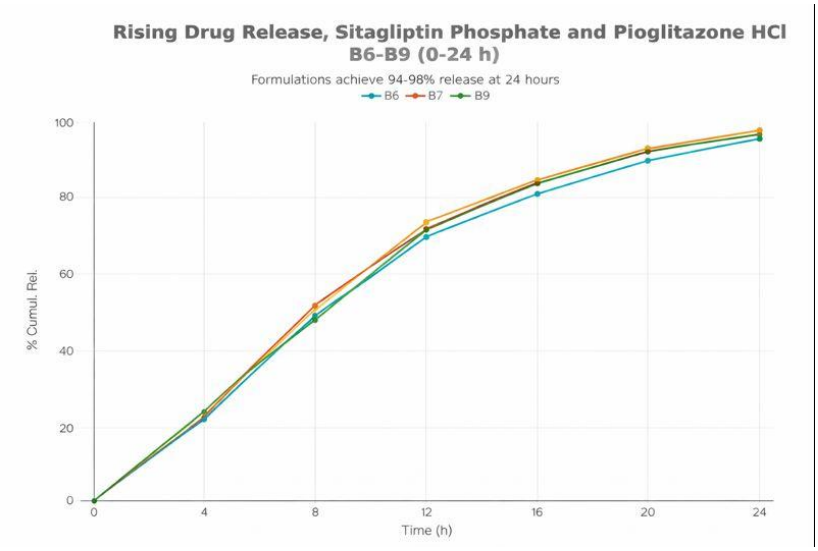
Time (hrs)	% Cumulative Drug Release								
	B1	B2	B3	B4	B5	B6	B7	B8	B9
0	0	0	0	0	0	0	0	0	0
4	19.4	20.1	22.4	26.1	27.2	28.5	29.5	29.8	28.6
8	48.8	50.3	47.6	48.1	52.3	47.9	51.1	52.6	53.4
12	67.4	70.3	69.7	68.4	70.3	73.4	68.6	69.5	67.9
16	77.5	81.3	81.3	82.5	85.7	83.6	86.4	89.3	82.4
20	86.3	89.1	90.2	89.4	86.4	94.5	92.2	94.6	93.3
24	94.1	95.6	92.7	94.2	95.9	97.5	98.1	99.2	98.6



A)



B)



E)

IV. Drug release of sitagliptin phosphate and pioglitazone hcl SR

A) Shows for (B1-B3)

B) Shows for (B4-B6)

C) Shows for(B6-B9)

Drug Release Kinetics

Dissolution data were fitted to various kinetic models to elucidate the mechanism of drug release. The sustained-release layer formulations showed a better fit to the Higuchi and Korsmeyer–Peppas models. The release exponent values indicated diffusion-controlled drug release, suggesting that drug diffusion through the swollen polymer matrix was the predominant release mechanism.

These findings confirm the effectiveness of hydrophilic polymers in regulating drug release and support their selection for sustained-release bilayer tablet formulation.

CONCLUSION

The findings of the current study have established the capability of preparing a sustained release bilayer tablet of gliclazide, pioglitazone hydrochloride, and sitagliptin phosphate using conventional techniques. The bilayer formulation successfully harnessed the benefits of both immediate and sustained release of the drug.

Optimized formula F9 made possible the creation of formulations with favorable physicochemical characteristics, controlled dissolution, and reproducible kinetic release, so

that it became a promising fixed-dose combination strategy for the chronic treatment of type 2 diabetes mellitus.

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