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Research Article

Formulation And Evaluation Of Bilayer Tablets For The Treatment Of Diabetes.

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ABSTRACT

This research was to formulate and evaluate bilayer tablets for the effective treatment of diabetes. Bilayer tablets, combining immediate and sustained-release layers, aim to provide a swift onset of action followed by prolonged therapeutic effects. The immediate-release layer was formulated using Metformin HCl, while the sustained-release layer contained Glipizide. Both layers were prepared using wet granulation and direct compression techniques. Reformulation studies, including drug-excipient compatibility and powder flow properties, were conducted to ensure stability and manufacturability. The bilayer tab is evaluated for its properties, like hardness, friability, weight variation, and thickness. Additionally, In vitro disso studies were performed to compare tab release profiles for the immediate and sustained-release layers. The immediate-release layer showed a rapid drug release within the first hour, ensuring quick therapeutic action. In contrast, the sustained-release layer exhibited a controlled release over 12 hours, maintaining steady plasma levels. Stability studies indicated that the bilayer tablets remained stable under accelerated conditions. The combination of Metformin HCl and Glipizide in a bilayer tablet offers an efficient therapeutic approach for managing diabetes by enhancing patient compliance through reduced dosing frequency and optimized drug release profiles.

Keywords: Bilayer tablets, diabetes treatment, Metformin HCl, Glipizide, controlled release

INTRODUCTION

Prior studies on this subject have shown that people with diabetes mellitus who contracted the 2019 coronavirus disease (COVID-19) had less than ideal-clinical outcomes. However, it seems as though there is a street of interaction between the two objects that runs in both directions (Schwartz S et al 2006). That which was previously stated is supported by this. The ongoing COVID-19 epidemic has had a big influence on diabetics' capacity to keep their blood glucose levels under control. Being able to regulate their blood sugar levels is one of these choices. This provides evidence in favor of what was previously said. The ability of diabetics to control their blood glucose levels has been significantly impacted by the current COVID-19 pandemic. One of these options is being able to control their blood sugar levels. Alternatively, "direct effects" refer to the effects that are directly linked to the viral infection. Referred to as direct repercussions, they are the effects directly associated with the sickness. This section covers the two most notable instances of indirect impacts. We include both of the instances here. One can consider the effects of these factors via two distinct lenses: direct and indirect perspectives. Any of these two perspectives can be used to analyze the situation. It has been demonstrated that patients with COVID-19 infection experience a significant change in their metabolic processes. It also results in significant increases in blood glucose levels in addition to this. This is what many have noticed. Increases in inflammatory mediators and cytokines have been linked to both insulin resistance

and concurrent hyperglycemia. Both of these events have been connected to these increased levels. The basic idea underlying this phenomenon is that it is produced by an increase in the production of inflammatory mediators and cytokines (Tripathi K.D et al 2004).

ADVANTAGES OF BILAYER TABLETS (James et al. 2007)

1 Bilayer tablets allow for combination therapy in a single pill by combining two distinct medications or formulations into one dosage form.
2 By providing various release patterns for both immediate and sustained medication release, they offer a comprehensive method of drug administration.
3 By separating incompatible ingredients into distinct layers, bilayer pills avoid medication interactions and preserve stability.
4 By providing exact control over the amount of every medication component, these tablets maximize therapeutic efficacy.
Bilayer tablets can result in long-term cost savings by optimizing production and distribution, even if they initially need more complicated manufacturing procedures.
In general, bilayer tablets improve patient convenience and treatment results by providing a flexible option for combination therapy.

DISADVANTAGES OF BILAYER TABLET

1. Complex manufacturing procedures increase production costs Risk of layer separation or delamination during production or storage.
2. Limited suitability for certain medications due to difficulties in achieving required release profiles.
3. Higher risk of dose dumping if one layer dissolves too quickly.
4. Potential regulatory obstacles related to proving compatibility, stability, and uniformity between layers.
5. Challenges in achieving uniform distribution and consistency of drug content between layers, leading to variations in therapeutic effects among batches.

METFORMIN HYDROCHLORIDE:

Metformin, the main treatment of diabetes which is type 2, functions may be lowering the amount of glucose the liver produces and raising the peripheral insulin system's sensitivity. It is given as immediate-release and extended-release tablets, among other forms. To minimize gastrointestinal side effects, titration must be done gradually. In rare situations of renal impairment, lactic acidosis, and other uncommon concerns necessitate regular monitoring of blood glucose levels and renal function. Still, given its good safety profile and ability to effectively lower blood glucose and HbA1c, it is unquestionably the first-choice medication for type II Diabetes. sustained importance of metformin in diabetes treatment regimens is highlighted by its accessibility and proven advantages (Annapuriddi et al 2019).

GLIPIZIDE:

An effective treatment for type 2 diabetes mellitus is glipizide, a sulfonylurea drug. Helping to regulate blood sugar, it induces the production of insulin from pancreatic beta cells. Doses are normally administered orally, though they can change depending on each person's reaction. Intestinal disruptions, allergy responses, and hypoglycemia are typical adverse effects. It may interfere with other medications, therefore people with compromised liver or renal function should use caution when using it. In cases of diabetic ketoacidosis, severe liver or renal dysfunction, type 1 diabetes, and during pregnancy or lactation, glipizide should not be used. It is advised that organ function and blood sugar levels be regularly monitored. For the best diabetic control, glipizide medication is used in conjunction with dietary and activity changes. For specific advice, always speak with a healthcare provider (IDF et al 2019).

MECHANISM OF ACTION OF BILAYER TABLETS

Bilayer tablets use two different formulations or active components in one tablet by using a complex process. These layers allow different therapy approaches and are frequently divided to avoid interactions. To improve patient compliance and dosage convenience, one layer may offer instantaneous release, while the other may offer regulated or sustained release. On the other hand, medications that need distinct absorption sites or intervals can benefit from the scheduled delivery provided by sequential release mechanisms. Facilitation simplifies regimens and boosts adherence to combination therapy. Maintaining stability and effectiveness requires careful formulation and excipient selection, as compatibility between layers is crucial. Bilayer tablets, therefore, provide a flexible approach to drug administration, meeting a range of release patterns and therapeutic requirements while maintaining efficacy and safety (Chatterjee et al 2017).

MATERIAL AND METHOD

MATERIALS

Metformin Hydrochloride and Glipizide raw material samples were gifted by Leeford Healthcare Ltd. (Ludhiana, Punjab) India. Tragacanth gum, Microcrystalline cellulose, Lactose, Polyvinylpyrrolidone, Magnesium Stearate, HPMC K100, Ethanol, Cyclodextrins. It was provided by Dev Bhoomi Uttarakhand University, Dehradun, pincode-248007. Sunset Yellow FCF Colour was purchased from the market (Alessio et al 2018).

Table no.1-Formulation of Metformin Sustain Release and Glipizide Immediate Release Bilayer Tablet Metformin hydrochloride contains layer

Component	Formulation A (mg)	Formulation B (mg)	Formulation C (mg)
Metformin	500	500	500
Microcrystalline cellulose (MCC)	220	175	270
Hydroxypropyl Methylcellulose (HPMC) 100KM	250	-	-
Hydroxypropyl Methylcellulose (HPMC) K15M	-	300	-
Hydroxypropyl Methylcellulose (HPMC) K4M	-	-	200
Silica Gelly	15	10	15
Magnesium Stearate	10	10	10
Total Weigh	995	995	995

Different Trial Formulations of the Glipizide-Containing Insult Layer

Component	Formulation A	Formulation B	Formulation C
API (mg)	5	5	5
Sodium Starch Glycolate(mg)	10	25	35
MCC (mg)	80	65	45
Talc(mg)	4	2	4
Lemon yellow(mg)	1	1	1
Total weight(mg)	100	100	100

METHOD

Preparation of Bilayer Tablet

Careful formulation development is required to assure compatibility and efficacy when combining metformin with glipizide in a bilayer tablet. The choice of suitable lubricants, disintegrants, and binders for every layer is determined by an initial evaluation of the excipient compatibility and solubility. Optimizing parameters for homogenous granules is achieved by granulating the medicines individually. Tablet hardness and stickiness can be adjusted during compression using a bilayer tablet press to create separate layers. To alter release kinetics, coating can be used. Adherence to the dissolution profile, consistency, and content are guaranteed by quality control tests. It's critical to follow good manufacturing practices. The procedure is finished with packaging in labels. Safety and efficacy criteria are maintained throughout by ongoing collaboration with formulation experts (Atkinson et al 2014).

UV SPECTROPHOTOMETRY-BASED METFORMIN HYDROCHLORIDE ESTIMATION

Preparation of Stock Solution

The phos-buff pH ^{6}.8 is used to mix the API accurately weighing 100 mg metformin hydrochloride then transferring that in a 100 ml volume flask. Phosp buff pH 6.8 is then used to make up the remaining volume to 100 ml, yielding the stock solution, which is 1000 µg/ml (Kahn et al 2014).

- **Getting the Standard Solution Ready**

Pipette 1 ml from the stock solution L into a 100 ml standard volumetric flask. Phosphate buffer pH 6.8 should be used to bring the volume up to 100 ml, yielding the stock solution ll (10µg/ml). Pipette 0.2, 0.4, 0.6, 0.8, and 10 ml of the stock solution ll into five distinct 10 ml volumetric flasks, respectively. Next, use phosphate buffer pH 6.8 to get the volume up to the required level to obtain concentration solutions with 2, four, eight, 10 µg/ml. poss buff pH 6.8 used a blank. At 233 nm, the absorb is measured, in the concentration (µg/ml) vs absorbance graph was generated (ADA et al 2022).

GLIPIZIDE ESTIMATION USING UV SPECTROPHOTOMETRY

• Preparation of Stock Solution

Phosphate buffer (pH 6.8), 100 mg of Glipizide, and the minimal minimum of methanol should all be carefully weighed and put into a 100 ml volumetric flask. After that, add enough phosphate buffer (pH 6.8) to make the volume reach 100 ml, which will yield the stock solution (1000 µg/ml).

• Creation of Benchmark Solution

With the stocked solution, pipette one milliliter (ml) then transfer it in a standard volume flask with a capacity of 100 ml. The stock solution ll (10µg/ml) can be obtained by adjusting the volume to 100 ml using phosphate buffer pH 6.8. Pipette the stock solution ll's 0, 2, four, six, eight, ten µg/ml concentrated solution into five different 10 ml volumetric flasks, in that order. Next, add phosphate buffer (pH 6.8) to the remaining volume to reach the required level. The blank was a phosphate buffer with a pH of 6.8. Plotting absorbance against concentration (µg/ml), 276 nm was the measured absorbance (ADA et al 2022).

COMPATIBILITY STUDIES

A drug material must be chemically and physically defined before being formulated into a dosage form. When combining medicine with pharmaceutical excipients to create a dosage form, compatibility studies provide the framework and information required to characterize the nature of the drug components. The compatibility of the chosen excipients or carriers is one of the prerequisites for pharmaceutical formulation. To determine whether there may be a chemical interaction between metformin and glipizide, as well as between the two drugs' excipients, an infrared spectrophotometer was used in the current experiment. The compatibility of the chosen excipients or carriers is one of the prerequisites for pharmaceutical formulation. To determine whether there may be a chemical interaction between metformin and glipizide, as well as between the two drugs' excipients, an infrared spectrophotometer was used in the current experiment. 100 micrograms of potash bromide (dried at 40–50C) and 3 mg of the medication were combined. A translucent pellet was formed by compressing the mixture in a hydraulic press at a pressure of 10 tons. Using a Silverstein IR spectrophotometer, pallets were scanned in four thousand-four hundred cm-I (ADA et al 2022).

Particle Size Distribution

We filled the top of the sieve set with 30 g of the powder combination. Following that, it was gently closed and let for ten minutes to sit in the sieve shaker. After considering the particle size, the weight difference between the sieve's pre- and post-agitation weights was calculated to find wt. off powder retained in all sieves. The particle size distribution graph was plotted as the final phase.

The angle of repose:

A funnel is secured inside the stand. We weighed powdered medicine, then transferred it into the funnel and sealed the entrance with our thumbs. The powder was then let to flow out when the thumb was removed. A circle was drawn around the edges, and a measurement of the height (h) was made to get diameter. in equation following were use for calculated to angles:

If r is the radius, then

tan-1 h/r = angle of repose (θ).

• Bulk density:

- Weighing the powder sample first, it was carefully added to a 50 ml (1.69 oz) graduated cylinder. After the sample's volume was noted, the sample weight was divided by volume to determine the bulked density or bd.

• Tapp Density:

- The measurement method involved 100 taps on the cylinder that held the sample. TD calculated the divide in sample wt. to its ultimate vol.

Carr's Index Formula:

- To determine Carr's index, one must first remove the bulk density from the tapped density, divide the result by the tapped density, and then multiply the result by 100 to get the percentage (Abdul et al. 2008, Aruna et al.2000).

Here's the formula expressed mathematically:

Carr's index = (Tapp density – Bulk Density x 100)/Tapped density.

Hausner's ratio:

was computed using The Following Formula: HR = Tapp Density/bulk Density.

Method for manufacturing bilayer tablet:

Materials and Methods

Preparation of Metformin Layer:

• Weighing and Mixing:

Metformin and the required excipients were accurately weighed using a precision balance. The weighed components were transferred to a mortar and pestle. The mixture was thoroughly blended to ensure uniformly distributed in the active pharmaceutics ingredient (API) with the excipients (Bailey CJ et al. 1996).

Preparation of Glipizide Layer:

• Weighing and Kneading:

The specified amount of Glipizide was weighed and placed in a Petri dish. A few drops of ethanol were added to the Glipizide to aid in the wet granulation process. A suitable coloring agent was also incorporated to distinguish the layers visually. The mixture was kneaded manually until a uniform consistency was achieved (Banker et al.1987).

• Drying:

The kneaded Glipizide mixture was spread evenly in the Petri dishes. The Petri dishes were place into a warm air oven preheated to 90°C. The mixture was dried until it reached a constant weight, indicating the removal of ethanol.

Compression of Bilayer Tablets:

• Compression of Metformin Layer:

The dried Metformin mixture was placed into the die cavity of a compression machine. The mixture was subjected to pre-compression to form a uniform and stable layer.

• Addition and Compression of Glipizide Layer:

The dried Glipizide mixture was carefully placed on top of the pre-compressed Metformin layer. The die was then subjected to final compression using a punching machine to form the bilayer tablet. The compression process ensured proper adhesion between the two layers, resulting in a stable bilayer tablet (D Choudhary et al.2009).

Evaluation of Bilayer Tablets:

The formulated bilayer tablets were evaluated for various physical and chemical parameters to ensure quality and efficacy. Parameters such as tablet hardness, friability, thickness, weight variation, and dissolution profile were assessed according to standard pharmacopeial methods.

Evaluation Parameter (Defang O et al. 2005, DeFronzo et al. 1995)

TABLETS

Following were the quality control tests performed on the prepared tablets:
Weight fluctuation
Durability
Dependability
homogeneity of drug content
Decomposition
Dissolution experiments in vitro

• Weight fluctuation

Weighing each of the twenty pills individually and figuring out their average weight is the process of performing the USP weight variation test. The weight of each tablet is then contrasted with this mean. If there are less than two tablets that depart from the permitted percentage limit and no tablet differs by more than twice this amount, the tablets pass the USP test. The USP standard states that tablets over 324 mg may have a weight variation of up to ±5%.

• Durability

The hardness of the tablet formulation was measured using a Pfizer hardness tester. The test was conducted on five randomly selected tablets.

• Dependability

The pre-weighed tablets undergo four minutes, or 100 revolutions, of falling inside a chamber. The tablets are dropped six inches to provide shock throughout each revolution. The tablets are weighed again after 100 spins to measure weight loss, which shows how friable they are. A maximum weight reduction of 0.5 to 1% is considered acceptable.

• **The homogeneity of drug content** 20 tablets by weight, ensuring accuracy. Take a sample containing approximately 1 gram of metformin and weigh it precisely. Shake this sample with 70 milliliters of water for 15 minutes, then dilute it to 100 milliliters with water and filter. Add 100 milliliters of water to 10 milliliters of the filtrate. Dilute 10 milliliters of this solution to 100 milliliters with water. Measure the maximum absorbance of the resulting solution at around 232 nm. Utilizing a specific absorbance value of 798determinesm, determine the content of metformin hydrochloride.

• Decomposition

The disintegration testing device is designed to handle six tablets simultaneously. The basket rack assembly features six glass tubes, each measuring three inches in length and open at the top, with a ten-mesh screen affixed to the bottom. Each tube contains one tablet for disintegration time measurement. The basket racks are placed 2.5 cm above the beaker's base and immersed in up to one liter of aqueous medium maintained at 37°C ± 2°C. A motor-driven mechanism operates the basket assembly, moving it up and down at a rate of 28–32 cycles per minute over a distance of 5–6 cm. To comply with United states pharmacopeia standards, every fragment of the tablet must pass through all ten mesh screens within the allotted time. For uncoated tablets, the US Pharmacopeia specifies a disintegration time of five minutes (Dunn et al 1995).

• Dissolution experiments in vitro

Metformin hydrochloride release kinetics from sustained-release tablets in 900 milliliters of dissolving media were assessed using a device known as the United States Pharmacopeia disso paddles equipment (Laboratory Indian Dissolution two thousand). Operating at fifty revolutions per minute, the device kept the temperature at 37 ± 0.5°C. The dissolving liquid used in this experiment was a 6.8 pH phosphate buffer. A sample of the dissolving fluid was taken at pre-arranged intervals, and its spectrophotometric absorbance at 233 nm was measured. Based on the information gathered, a graph showing time vs the percentage of medicines released was created (Fassihi et al 1993).

Result and Discussion

UV SPECTROPHOTOMETRY-BASED EXACT METFORMIN HYDROCHLORIDE EXTRACT

pH 6.8 phosphate buffer was used to quantify the amount of metformin hydrochloride, and UV spectrophotometry was used to measure the compound at 233 nm. Between 2 and 10µg/ml, it complied with Beer's legislation. The findings, which are shown in Table 1, showed that the correlation coefficient was 0.9999 and the slope was 0.0784 (Ganesh et al 2007, G. Mubeen et al 2009).

Table 1: UV spectrophotometry-based estimation of 233 nanometers of metformin hydrochloride

S. Number.	Conc. µg/ml	Absorb At 233 nm
1	0	0
2	2	0.143
3	4	0.290
4	6	0.465
5	8	0.612
6	10	0.773

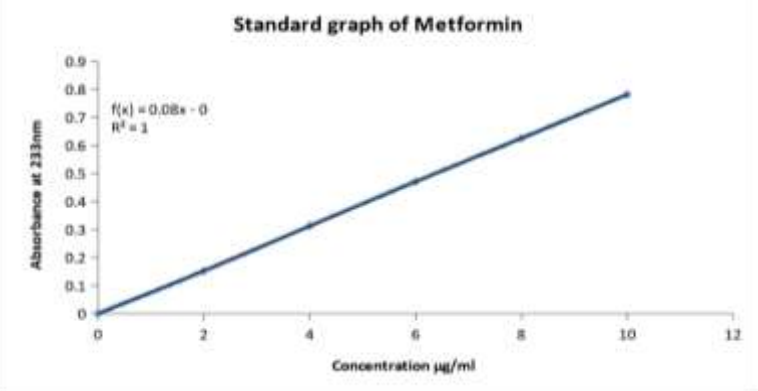


Fig. 1: UV spectrophotometry estimation of 233 nanometers of metformin hydrochloride

Use of photos buff p^H 6.8, the amount of glipizide were approximated, and UV spectrophotometry was used to measure it at 276 nm. In the 2–10µg/ml range, it complied with Beer's law. The findings are shown in Table 2 and show that the slope was 0.023 and the correlation coefficient was 0.9997.

Table 2: UV spectrophotometric estimation of Glipizide at 276 nm (Higuchi et al 1962)

S.Number.	Concentration µg/ml	Absorbance At 276 nm
1	0	0
2	2	0.044
3	4	0.089
4	6	0.138
5	8	0.179
6	10	0.228

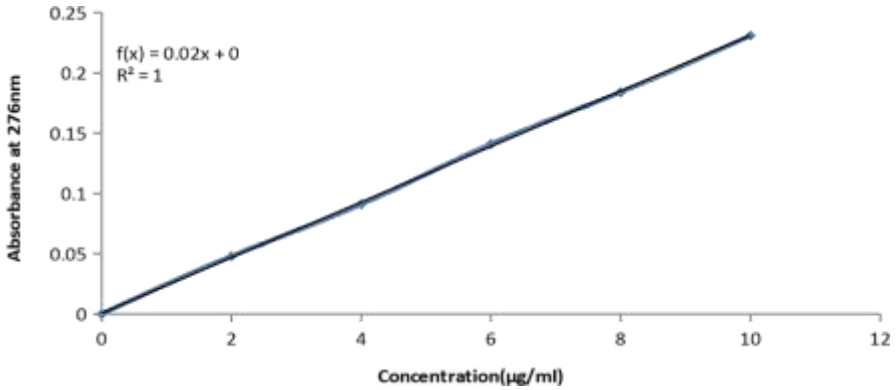
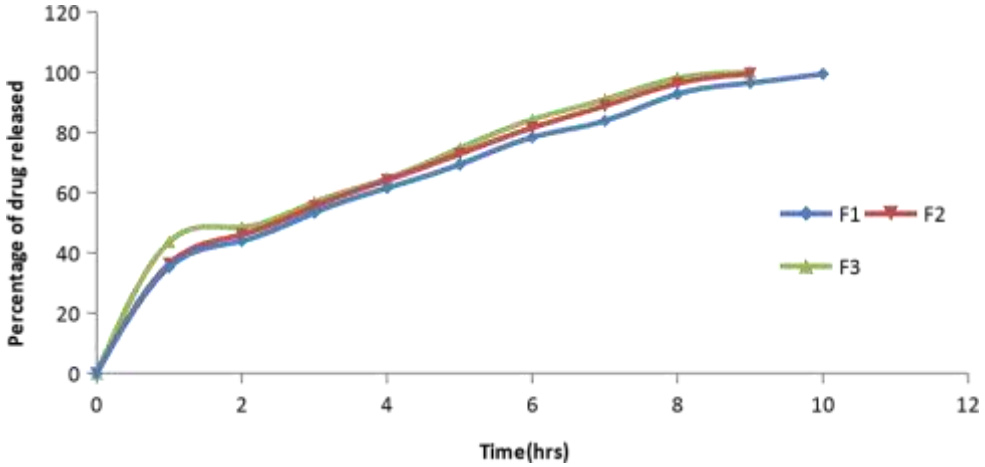


Fig. 2: UV spectrophotometry estimation of Glipizide at 276 nm.

Metformin hydrochloride tablets: drug release kinetics



Metformin hydrochloride SR tablets: Zero-order and First-order releases (Korsmeyer et al 2007)

F¹, F², F³

Formulation	0 order R^2	1st order R^2	Higuchi's Kinetic R^2	Korsemeyer's Kinetic R^2
Formula1st	0.921	0.821	0.989	0.986
Formula2nd	0.979	0.801	0.988	0.981
Formula3rd	0.892	0.826	0.970	0.951

Summary

This research paper focuses on the formulation and evaluation of bilayer tablets designed for the effective treatment of diabetes. The primary objective was to create a tablet that combines immediate and sustained-release properties, ensuring rapid onset and prolonged therapeutic effects. The immediate-release layer of the tablet contains Metformin HCl, which provides quick therapeutic action, while the sustained-release layer contains Glipizide, ensuring a controlled release over an extended period. The preparation of the bilayer tablets involved wet granulation and direct compression techniques. Reformulation studies, such as drug-excipient compatibility and powder flow properties, were conducted to ensure the stability and manufacturability of the tablets. The physical properties of the bilayer tablets, including hardness, friability, weight variation, and thickness, were evaluated to meet standard pharmaceutical criteria. In vitro dissolution studies were carried out to analyze the drug release profiles of both layers. The results indicated that the immediate-release layer achieved rapid drug release within the first hour, while the sustained-release layer maintained a controlled

drug release for up to 12 hours. Stability studies under accelerated conditions confirmed the stability of the bilayer tablets. The combination of Metformin HCl and Glipizide in a bilayer tablet presents a promising therapeutic approach for diabetes management. This formulation not only enhances patient compliance by reducing the dosing frequency but also optimizes the drug release profiles to ensure effective blood glucose control (Hogan et al 1989, Hsieh SH et al 2006).

Conclusion

A major advancement in the treatment of diabetes has been made with the development of bilayer tablets containing Glipizide and Metformin. Metformin was carefully weighed, combined with excipients, and then kneaded with ethanol and a coloring agent. Glipizide was then dried at 90°C to guarantee stability and homogeneity. Two steps were taken in the compression of the bilayer tablets: first, the Metformin layered was compressed, and the Glipizide layer was added and then compressed. This process guaranteed tablets' coherence and durability. Thorough assessments verified that the tablets satisfied pharmacopeial requirements concerning hardness, friability, thickness, variance in weight, and dissolution characteristics. By combining two medications into a single dose and preserving the stability and efficacy of both, this bilayer tablet formulation has various benefits, including improved patient compliance. An API. Additionally, distinct release profiles are possible thanks to the bilayer architecture, which enhances therapeutic results. Pharmacokinetic and pharmacodynamic qualities should be evaluated in vivo by conducting experiments and scaling up the formulation process in future research. About enhancing patient adherence and treatment efficacy, the creation of these bilayer tablets in the positive forwarded fields of combination therapy for diabetes.[19-20]

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