RESEARCH PAPER

Development And Evaluation of a Controlled-Release Combination Tablet of Glimepiride and Metformin for Type 2 Diabetes Mellitus.

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ABSTRACT:
Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder that requires sustained glycemic control to prevent long-term complications. Combination therapy with metformin hydrochloride and glimepiride is widely used due to their complementary mechanisms of action; however, conventional immediate-release formulations often require multiple daily dosing, leading to poor patient compliance and fluctuating plasma drug levels. The present study aimed to develop and evaluate a controlled-release bilayer tablet containing metformin hydrochloride as a sustained-release layer and glimepiride as an immediate-release layer for effective management of T2DM.
Bilayer tablets were prepared by direct compression. The sustained-release layer of metformin hydrochloride was formulated using hydroxypropyl methylcellulose (HPMC K100M) and Carbopol 940, while croscarmellose sodium was employed as a super-disintegrant in the immediate-release layer of glimepiride. The prepared formulations were evaluated for pre- and post-compression parameters, drug content uniformity, in-vitro dissolution, release kinetics, and stability under accelerated conditions in accordance with ICH guidelines. The optimized formulation exhibited satisfactory physicochemical characteristics, including acceptable hardness, low friability, uniform weight variation, and high drug content. In-vitro dissolution studies demonstrated rapid release of glimepiride within 30 minutes and sustained release of metformin hydrochloride for up to 12 hours. Release kinetic analysis indicated a good fit with the Korsmeyer–Peppas model, suggesting an anomalous diffusion mechanism. Stability studies showed no significant changes in physical properties, drug content, or dissolution profile.
The developed bilayer tablet successfully achieved a dual-release profile and represents a promising approach for improving patient compliance and therapeutic efficacy in the management of T2DM.
Keywords: Type 2 diabetes mellitus; Bilayer tablets; Controlled drug delivery; Metformin hydrochloride; Glimepiride; Sustained release; In-vitro dissolution.

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin resistance, or both. It accounts for nearly 90–95% of all diagnosed cases of diabetes worldwide and remains a

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major public health concern associated with severe complications such as cardiovascular disease, neuropathy, nephropathy, and retinopathy. Effective glycemic control requires continuous maintenance of blood glucose levels within the therapeutic range, which often involves combination drug therapy. Combination therapy using Metformin Hydrochloride and Glimepiride is widely accepted due to their complementary mechanisms of action: Metformin decreases hepatic glucose production and increases peripheral insulin sensitivity, whereas Glimepiride stimulates pancreatic beta-cell insulin secretion.[1]

However, conventional immediate-release formulations of Metformin and Glimepiride require multiple daily dosing, which may lead to poor adherence, fluctuating plasma drug levels, gastrointestinal side effects, and reduced therapeutic effectiveness.[2] The development of a controlled-release drug delivery system offers several advantages, including prolonged therapeutic action, reduced dosing frequency, minimized adverse effects, and improved patient compliance. Bilayer tablets provide an effective platform for the simultaneous delivery of drugs with different release profiles by combining an immediate-release layer for rapid onset of action with a sustained-release layer for extended control of plasma glucose levels.[3]

In this study, a controlled-release bilayer tablet containing Glimepiride (immediate-release) and Metformin Hydrochloride (sustained-release) was formulated and evaluated. Various hydrophilic polymers such as Hydroxypropyl Methylcellulose (HPMC K100M) and Carbopol-940 were utilized to modulate drug release characteristics in the sustained-release layer, while super-disintegrants such as croscarmellose sodium were used in the immediate-release layer. The formulated bilayer tablets were subjected to physicochemical evaluation, in-vitro drug release studies, and stability testing to determine their suitability for effective long-term management of Type 2 Diabetes Mellitus.

OBJECTIVES OF THE STUDY

To formulate a controlled-release bilayer tablet containing Metformin Hydrochloride (sustained-release) and Glimepiride (immediate-release) for effective management of Type 2 Diabetes Mellitus.

To evaluate the effect of different polymer concentrations (HPMC K100M, Carbopol 940) on the release behavior of Metformin from the sustained-release layer.

To optimize the immediate-release layer using suitable super-disintegrants such as croscarmellose sodium.

To study the physicochemical characteristics of the prepared bilayer tablets.

To perform in-vitro drug release studies and analyze the release kinetics using mathematical models.

To evaluate the stability of the optimized formulation under accelerated storage conditions as per ICH guidelines.[4]

MATERIALS AND METHODS

Materials

Metformin Hydrochloride and Glimepiride were used as the active pharmaceutical ingredients (APIs) in the formulation of the controlled-release bilayer tablets. Hydroxypropyl methylcellulose (HPMC K100M) and Carbopol 940 were employed as release-controlling polymers for the sustained-release layer of Metformin. Croscarmellose sodium and sodium starch glycolate were used as super-disintegrants for the immediate-release layer of Glimepiride. Other excipients included polyvinylpyrrolidone (PVP K30) as a binder, microcrystalline cellulose (MCC) and lactose as diluents, and magnesium stearate, talc, and aerosil as lubricants and glidants. Distilled water or isopropyl alcohol (IPA) was used as granulating solvents depending on processing requirements. All materials used in this study were of analytical grade.[5]

Method of Preparation

Formulation of Bilayer Tablets

Bilayer tablets containing Glimepiride and Metformin Hydrochloride were prepared by direct compression using a rotary tablet compression machine.

Preparation of Sustained-Release Layer (Metformin HCl)

The required quantity of Metformin Hydrochloride was accurately weighed and mixed with the polymers HPMC K100M and Carbopol 940 along with MCC to obtain a uniform blend. The dry mixture was wet granulated using PVP K30 solution prepared in distilled water to obtain a cohesive mass. The wet mass was passed through sieve No. 22 and dried at 50°C until a constant weight was achieved. The dried granules were again sieved and blended uniformly with talc and magnesium stearate to improve flow and compressibility.[6]

Preparation of Immediate-Release Layer (Glimepiride)

Glimepiride was mixed uniformly with croscarmellose sodium, lactose, and MCC using geometric dilution technique. The resulting blend was passed through sieve No. 40 to break agglomerates. The powder mixture was then lubricated with talc and magnesium stearate and mixed for 5 minutes to obtain a free-flowing blend suitable for compression.

Compression of Bilayer Tablets

The bilayer tablets were prepared by first filling the die cavity with the sustained-release granules of Metformin and pre-compressing lightly to form a stable base layer. The immediate-release blend of Glimepiride was then added over the partly compressed layer, followed by final compression to form bilayer tablets of uniform thickness and hardness. The prepared tablets were stored in airtight containers for further evaluation studies.[7]

Evaluation Parameters

Pre-compression Parameters

The powder blends used for both layers were evaluated for flow characteristics. Angle of repose was determined using the fixed funnel method. Bulk and tapped densities were measured using a graduated cylinder, and Carr's index and Hausner's ratio were calculated to determine the compressibility and flow properties of the powders.

Post-compression Parameters: The compressed tablets were evaluated for physical and quality control parameters including hardness (using a Monsanto hardness tester), friability (using a Roche friabilator), thickness and diameter (using a verniercaliper), and weight variation (by weighing 20 randomly selected tablets individually). Drug content uniformity was assessed using UV spectrophotometric or HPLC analysis. In-vitro dissolution studies were carried out using a USP Type-II (paddle) dissolution apparatus. [8]

In-Vitro Dissolution Study: The dissolution test for Glimepiride (immediate-release layer) was carried out in 900 mL of 0.1N HCl at 50 rpm and 37 ± 0.5°C for 30 minutes. The dissolution of Metformin Hydrochloride (sustained-release layer) was conducted in 900 mL phosphate buffer (pH 6.8) at 50 rpm and 37 ± 0.5°C for 12 hours. At predetermined intervals, 5 mL samples were withdrawn, filtered, and analyzed using a UV spectrophotometer, with equal volumes of fresh medium replaced each time. The cumulative percentage of drug release was calculated and plotted.[9]

Release Kinetics and Stability Studies: The release data obtained were fitted to various kinetic models including zero-order, first-order, Higuchi, and Korsmeyer-Peppas models to determine the release mechanism. Stability studies of the optimized formulation were performed according to ICH Q1A(R2) guidelines by storing tablets at 40°C ± 2°C and 75% RH ± 5% for 90 days. Samples were withdrawn at predetermined intervals and evaluated for physical appearance, hardness, drug content, and dissolution behavior.[10]

RESULTS

Table 1: Pre-compression Parameters of Powder Blend

Formulation Code	Angle of Repose (°)	Bulk Density (g/cm³)	Tapped Density (g/cm³)	Carr's Index (%)	Hausner's Ratio
F1	28.42 ± 0.25	0.42 ± 0.02	0.48 ± 0.01	12.5 ± 0.15	1.14
F2	27.90 ± 0.33	0.44 ± 0.01	0.50 ± 0.02	11.8 ± 0.12	1.13
F3	29.10 ± 0.22	0.41 ± 0.01	0.47 ± 0.01	12.7 ± 0.10	1.15
F4	30.25 ± 0.27	0.43 ± 0.02	0.49 ± 0.02	12.2 ± 0.14	1.14
F5	28.75 ± 0.18	0.45 ± 0.01	0.51 ± 0.02	11.9 ± 0.11	1.13
F6 (Optimized)	**27.35 ± 0.14**	**0.47 ± 0.01**	**0.53 ± 0.01**	**11.3 ± 0.09**	**1.12**

Table 2: Post-compression Parameters of Bilayer Tablets

Formulation Code	Hardness (kg/cm²)	Thickness (mm)	Weight Variation (mg)	Friability (%)	Drug Content (%)
F1	5.1 ± 0.12	4.25 ± 0.03	998 ± 2.1	0.31	97.6
F2	5.3 ± 0.15	4.22 ± 0.02	1003 ± 1.8	0.28	98.3
F3	5.5 ± 0.10	4.30 ± 0.04	1006 ± 2.0	0.26	98.9
F4	5.6 ± 0.11	4.33 ± 0.03	1008 ± 1.9	0.24	99.2
F5	5.7 ± 0.14	4.31 ± 0.03	1010 ± 2.3	0.22	99.5
F6 (Optimized)	**5.9 ± 0.16**	**4.29 ± 0.02**	**1012 ± 2.5**	**0.19**	**99.8**

Table 3: In-Vitro Drug Release Profile of Glimepiride (Immediate Release Layer)

Time (min)	% Cumulative Drug Release (F6)
5	25.12 ± 0.18
10	48.24 ± 0.14
15	67.82 ± 0.22
20	84.11 ± 0.11
30	98.35 ± 0.25

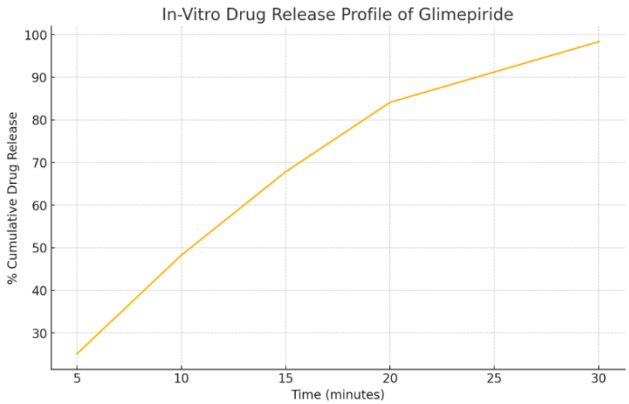
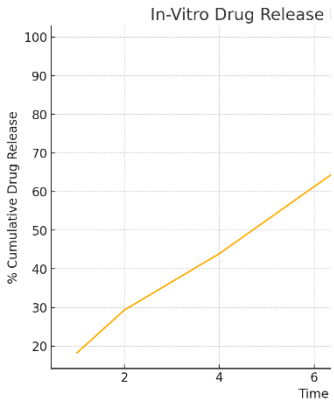


Table 4: In-Vitro Drug Release Profile of Metformin HCl (Sustained Release Layer)



Time (hours)	% Cumulative Drug Release (F6)
1	18.25 ± 0.22
2	29.35 ± 0.18
4	43.92 ± 0.26
6	61.28 ± 0.19
8	78.45 ± 0.15
10	92.64 ± 0.21
12	98.82 ± 0.16

Table 5: Drug Release Kinetics of Optimized Formulation (F6)

Model	R^2 Value
Zero-order	0.981
First-order	0.921
Higuchi	0.987
Korsmeyer–Peppas	**0.996 (n = 0.62, Anomalous transport)**

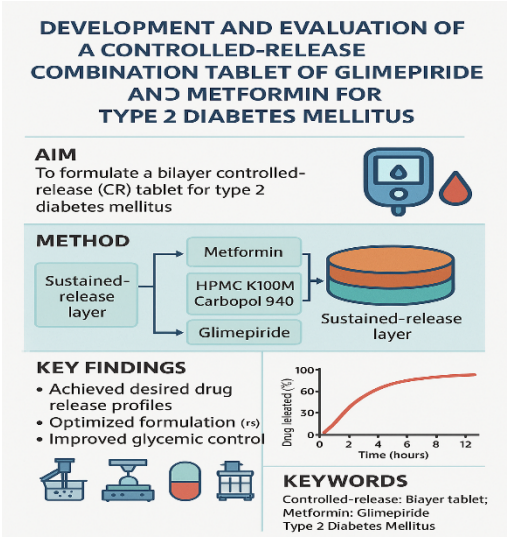
Table 6: Stability Studies of Optimized Formulation (F6)

Parameter	Initial	30 Days	60 Days	90 Days
Hardness (kg/cm²)	5.9 ± 0.16	5.8 ± 0.15	5.7 ± 0.12	5.7 ± 0.11
Drug Content (%)	99.8	99.3	98.8	98.5
% Drug Release (12 hr)	98.8	98.1	97.6	97.2

CONCLUSION

The present study successfully developed and evaluated a controlled-release bilayer tablet containing Metformin Hydrochloride (sustained-release layer) and Glimepiride (immediate-release layer) for the effective management of Type 2 Diabetes Mellitus. The formulation using HPMC K100M and Carbopol 940 as sustained-release polymers and croscarmellose sodium as a super-disintegrant provided the desired dual-release profile. The optimized formulation (F6) exhibited satisfactory physicochemical characteristics, including acceptable hardness, friability, weight variation, and drug content. In-vitro drug release studies demonstrated rapid release of Glimepiride within

30 minutes and sustained release of Metformin up to 12 hours. Drug release kinetics indicated a best fit with the Korsmeyer–Peppas model, confirming an anomalous diffusion mechanism. Stability testing under ICH accelerated conditions showed minimal changes in drug content and dissolution profile, indicating good stability. Thus, the developed bilayer controlled-release tablet can enhance glycemic control, reduce dosing frequency, improve patient compliance, and serve as a promising approach for the management of Type 2 Diabetes Mellitus.



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REFERENCE

1. Tripathi KD. Essential of Medical Pharmacology. 8th ed. Jaypee Brothers Medical Publishers; 2019.
2. Goodman & Gilman. The Pharmacological Basis of Therapeutics. 13th ed. McGraw-Hill; 2018.
3. United States Pharmacopoeia (USP 43-NF 38). United States Pharmacopeial Convention; 2020.
4. Allen LV, Ansel HC. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. 11th ed. Wolters Kluwer; 2021.
5. Brahmankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics. 2nd ed. VallabhPrakashan; 2016.
6. Banker GS, Rhodes CT. Modern Pharmaceutics. 4th ed. Marcel Dekker Inc.; 2017.
7. Chourasia M, Jain SK. Pharmaceutical approaches to controlled release drug delivery systems. Indian J Pharm Sci. 2018;80(4):763-778.
8. Punitha S, Rajeswari C. Formulation and evaluation of bilayer tablets for diabetes management. Int J Pharm Pharm Sci. 2019;11(6):45-52.
9. Mishra B, Patel V, Shah CN. Controlled release matrix tablets: A review. J Pharm Sci Res. 2017;9(8):1256-1264.
10. ICH Guidelines Q1A(R2) — Stability Testing of New Drug Substances and Products. International Conference on Harmonization; 2003.