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Research Article

# Bilayer tablet formulation of metformin hydrochloride and glimepiride: A novel approach to improve therapeutic efficacy

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## Abstract

The present research work was an attempt to design a formulation to improve the oral therapeutic efficacy with optimal control of plasma drug level which contains two antidiabetic drugs i.e Metformin HCl and Glimepiride. Bilayer tablet formulation has been developed consisting of two drug containing layers which comprises Metformin sustained release layer and an immediate release layer of Glimepiride was optimised separately and constituted in bilayer tablet, a common analytical method for quantitative combined drug estimation was employed and evaluated. Two different matrix formulations were developed, one matrix layer with hydrophilic swellable polymer and another with hydrophobic polymer as carriers for sustained drug delivery from matrices and were evaluated. Hydroxypropylmethylcellulose and Polyethylene oxide was used as polymers in order to get the sustained release profile over a period of 24 h. Tablets were evaluated for physical properties; drug content and in vitro drug release were compared with standard commercial tablets (Glimy-M). The excipients used in this formulation did not alter physicochemical properties of drug, as tested by HPLC, DSC, and FTIR. Stability of the drug release profiles at 6 months in 40˚C and 75%RH suggesting that HPMC based sustained release formulation was stable than the Polyethylene oxide sustained release formulation due to its stable and better targeting profile in terms of drug release. This formulation also exhibited the best fitted formulation into zero order kinetics and non-Fickian transport of the drug from the tablets was confirmed. Bilayer tablet prepared from optimised formula was found to be best suited method for fixed dose combination of sustained release Metformin HCl and immediate release Glimepiride.

**Keywords:** Sustained release, Metformin HCl, Glimepiride, Matrix formulation

## Introduction

The objective of this research project was to develop a combination drug therapy for antidiabetic tablet formulation having different mechanism of action to complement each other and together effectively lower blood glucose level.Metformin and glimepiride simultaneously targets insulin resistance and insulin deficiency of type 2 diabetes, which may account for the greater effects on glycaemia.Glimepiride maintains a more physiologic regulation of insulin secretion and the risk of hypoglycemia is less than with other sulfonylureas[1].

Metformin as extended release form and glimepiride as immediate release form were separately developed by wet granulation process and combined in a bilayer tablet form. Metformin extended release form was prepared by matrix system where two matrix formulations were developed, one by using hydrophobic polymer and another by using hydrophilic matrix system. i.e PEO and HPMC. The ability of hydrophobic and hydrophilic polymer (Polyethylene oxide and Hydroxypropylmethylcellulose) to act as a release controlling matrix for highly water soluble metformin were studied in order to design a tablet that would release over a period of 24 hours. Therefore, it is more logical to add another drug than replace the existing drug. The rapid introduction of combination therapy with two or three complementary oral anti diabetics help in targeting the dual effect and also reduced adverse effects[2].

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**Table 1: Formulation of bilayer tablet**

| Name | Manufacturer | Location of Manufacturer |
|---|---|---|
| Glimepiride | Wockhardt Research Centre | Aurangabad, India |
| Avicel pH 101 | FMC Biopolymer | Philadelphia, PA, USA |
| Lactose Monohydrate | DMV-Fonterra excipients | India |
| Povidone (Kollidon K25) | BASF South East Asia | India |
| Polysorbate 80 | Croda Inc, USA | USA |
| Sodium Starch Glycolate | DMV-Fonterra excipients | India |
| Magnesium stearate | Ferro Industries | Quimicas, Portugal |
| Metformin HCl | Wockhardt Research Centre | Aurangabad, India |
| Povidone (Kollidon K90) | BASF South East Asia | India |
| Polyox WSR 301 | Colorcon Asia Pvt. Ltd. | India |
| Polyox WSR N80 | Colorcon Asia Pvt. Ltd. | India |
| HPMC K100 M | Colorcon Asia Pvt. Ltd. | India |
| Sodium CMC | Signet Chemical Corporation | India |

Glimepiride are commercially available in Indian market. The conventional formulations containing 500 mg of Metformin hydrochloride are used in diabetes, at a dosing schedule of 3 to 4 times a day. The controlled release tablets of Metformin hydrochloride containing 500 mg of Metformin hydrochloride are prescribed as once a day formulations. The major benefits of controlled release Metformin hydrochloride tablets over conventional Metformin hydrochloride tablets include reduced dosing frequency and decreased incidence of gastro-intestinal side effects. It will improve patient compliances and will be highly acceptable by the patients.

Metformin and glimepiride tablets simultaneously targets insulin resistance and insulin deficiency of type 2 diabetes, which may account for the greater effects on glycaemia. Glimepiride maintains a more physiologic regulation of insulin secretion and the risk of hypoglycemia is less than with other sulfonylureas.

## Material and Methods

Glimepiride granules are formulated as immediate release layer and Metformin HCl granules are formulated as extended release layer for bilayer tablets.

Two different Metformin HCl extended release granules were prepared using two different techniques[2-4].

1. Matrix System.
2. Encapsulation System.

Bilayer tablets were prepared from both the extended release formulations and compared.

**Preparation of Bi layer tablets**

Two types of bilayer tablets were prepared as mentioned below

1. Using PEO based Metformin HCl ER granules as 1st layer and Glimepiride IR granules as 2nd layer.
2. Using HPMC based Metformin HCl ER granules as 1st layer and Glimepiride IR granules as 2nd layer.

Bilayer tablet compression machine (Cadmach, Ahmedabad) was used to press bilayer tablets.'D' tooling standard concave punches of 19.00 × 9.00 mm diameter was used. Extended release granules of Metformin HCl (1070 mg) were compressed first as 1st layer followed by immediate release granules of Glimepiride for second layer (170 mg). Tablets were collected during compression for in-process testing

**Evaluation of Tablets**

**Weight Variation**

Twenty (20) tablets from each batch were individually weighed in grams (gm) on an analytical balance. The average weight, standard deviation and relative standard deviation were reported. The tablet compression machine was suitably adjusted to produce tablets of uniform weight.

**Tablet thickness**

The thickness in millimetres (mm) was measured individually for 10 preweighed tablets by using a starrett portable dial hand micrometer. The average thickness, standard deviation and relative standard deviation were reported.

**Tablet hardness**

Tablet hardness was measured using a Key hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kilopond (KP) and the average hardness, standard deviations, and relative standard deviations were reported. Tablets hardness was checked at the start and during the compression process to control an acceptable range of tablet hardness.

**Uniformity of dosage units**

This was assessed according to the USP requirements <905> for content uniformity. The batch meets the USP requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 85% to 115% of the label claim and the RSD is less than or equal to 6%. According to the USP criteria, if one of these conditions is not met, an additional 20 tablets need to be tested. Not more that 1 unit of the 30 tested should be outside the range of 85% and 115% of the label claim and no unit outside the range of 75% to 125% of label claim. For all RSD should not exceed 7.8%.

**Friability**

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets were rotated at 25 rpm for 4 minutes (100 rotations) in the VanKel tablet friabilator. The tablets were then will dust and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets

***In vitro* drug release**

In vitro drug release was performed for the manufactured tablets according to the USP 26 "Dissolution procedure" <711>, over a 24-hour period for Metformin HCl ER and 1-hour for Glimepiride IR , using an automated Van Kel paddle dissolution system. A minimum of 6 tablets per batch were tested. The dissolution of Metformin HCl ER and Glimepiride IR from bilayer tablets was monitored using an automated VK 7010 dissolution tester coupled to an automated VK 8000 sample collector. The USP 24 (apparatus 2) paddle method was used at 50 rpm. The media used was 0.1N HCl at a pH 2.0 and a volume of 750 ml for the first 2 hours after which 250 ml of 0.2 M sodium phosphate, tribasic, was added to give a final pH of 6.8 and maintained at 37+ 0.5˚C.

Metformin HCl and Glimepiride release from each bilayer tablet (in the dissolution samples) was determined by high performance liquid chromatography (HPLC). The HPLC equipment was the Hewlett-Packard series 1100 equipped with a built in degasser, an auto sampler and a variable wavelength UV-VIS detector.

The column used was an XTerra Rp18, 5µm particle, 15 cm X 4.6 mm id equipped with a 4.6 mm X 2 cm guard column.

The HPLC conditions were as follows:

Mobile Phase: 65% 0.1 N Acetic Acid: 35% Methanol

Flow Rate: 1.0 ml/min

Detection: λ = 280 nm

Injection Volume: 20 µl

Metformin HCl and Glimepiride are normally analyzed by reversed-phase high performance liquid chromatography (HPLC) with ultraviolet (UV) detection. The amine functional group in the compound produces tailing peaks on much silica based stationary phases unless ion pairing agents are added. This method employs a specially deactivated stationary phase to minimize tailing effects and eliminates the need for modifiers in the mobile phase. The method employs the same detection wavelength, 280 nm, as the USP assay method for Metformin HCl and Glimepiride.

Different dissolution profiles were compared to establish the effect of formulation or process variables on the drug release as well comparison of the test formulations to the marketed product. The dissolution similarity was assessed using the FDA recommended approach (f2 similarity factor) (Food and Drug Administration 1997b). The similarity factor is a logarithmic, reciprocal square root transformation of the sum of squared errors, and it serves as a measure of the similarity of two respective dissolution profiles:

**Figure 1**

**Dissolution profile of Glimepiride Immediate Release Layer (F-I, F-II, F-III and Marketed Product)**

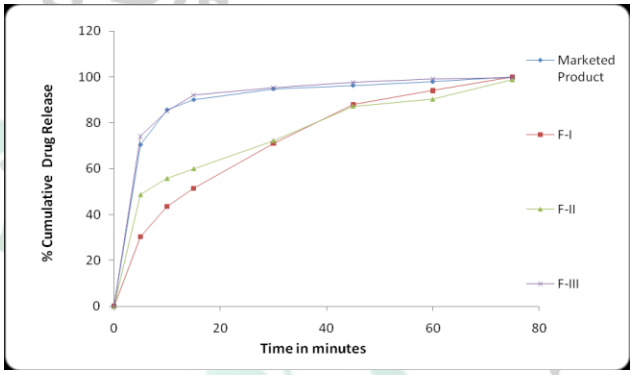
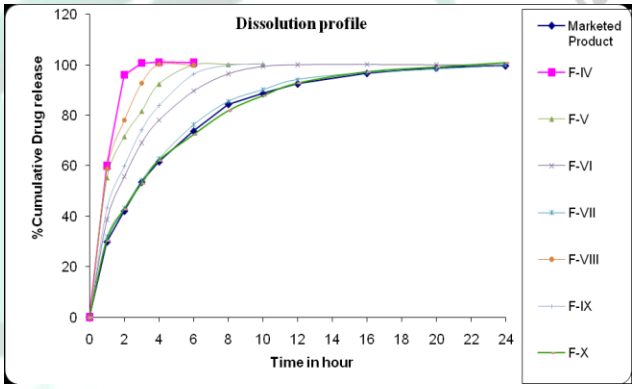



**Figure-2**

**Dissolution profile of Metformin Sustained Release Layer (F-IV, F-V, F-VI, F-VII, F-VIII, F-IX, F-X and Marketed Product)**




**Assay of Metformin Hydrochloride by HPLC**

**Standard Preparation:** Metformin Hydrochloride working standard equivalent to 50 mg were taken into100ml volumetric flask and it was diluted with Methanol and acetonitrile and mixed.

**Test Preparation:** Ten tablets of bilayer formulation, containing polyethylene oxide and Hydroxypropylmethylcellulose were weighted individually, both the formulation were taken separately and crushed into a fine powder by pestle in a mortar. The Metformin layer containing polymer Polyethylene was extracted by putting power equivalent to 125 mg of Metformin Hydrochloride in 250ml mixture of methanol and acetonitrile with 30 minutes sonication followed by shaking in between, sonication at 3000rpm for 10 minutes were carried out. The actual drug content for Metformin formulation containing polyethylene oxide was carried out by HPLC (High Performance Liquid Chromatography, 2695, Waters). Hypersil BDS c8, 125×4.6mm, 5$\mu$ column was used, Flow rate at 1.5 ml per minutes, load 20 $\mu L$ , at wavelength 233 nm with run time15 minutes. The actual drug content of Metformin layer containing Hydroxypropylmethylcellulose was carried out by HPLC (High

Performance Liquid Chromatography, 2695, Waters). Whatmann Partisil 10 SCX, 250 × 4.6mm ID column was used, Flow rate at 1.5 ml per minutes, load 10 $\mu L$ , at wavelength 233 nm with run time15 minutes.

**Assay of Glimepiride layer**

**Standard Preparation:** Glimepiride working standard equivalent to 40 mg were taken in to100ml volumetric flask and it was diluted with Methanol and acetonitrile and mixed. 5 ml was transferred in to 50ml volumetric flask and to this 10 ml of water was added. The volume was diluted with methanol and acetonitrile mixture in 50:50 ratios and was mixed.

**Test Preparation:** Ten tablets of bilayer formulation, containing Glimepiride were weighted individually crushed into a fine powder by pestle in a mortar. Glimepiride blend equivalent to 10mg was taken in 250ml volumetric flask. 25 ml of water was added to it and sonicated for 3 minutes. 125 ml mixture of methanol and acetonitrile in 50:50 ratios were added with 30 minutes sonication followed by shaking in between, centrifugation at 3000rpm for 10 minutes were carried out. The volume was made adding the methanol and acetonitrile mixture. Assay was carried out by HPLC (High Performance Liquid Chromatography, 2695, Waters). Hypersil BDS C18, 150×4.6mm, 5$\mu$ column was used, Flow rate at 1.5 ml per minutes, load 10$\mu L$ , at wavelength 226 nm with run time15 minutes

**Table 2:Composition of Glimepiride IR tablets 1mg**

| Wet granulation by RMG | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Batch No** | | **F-I** | | **F-II** | | **F-III** | |
| **S/N** | Granulation | mg/Tab | %w/w | mg/Tab | %w/w | mg/Tab | %w/w |
| 1 | Glimepiride | 1.00 | 0.59 | 1.00 | 0.59 | 1.00 | 0.59 |
| 2 | Avicel pH 101 | 66.00 | 38.82 | 92.00 | 54.12 | 86.00 | 50.59 |
| 3 | Lactose Monohydrate | 91.00 | 53.53 | 62.00 | 36.47 | 70.00 | 41.18 |
| 4 | Kollidon K25 | 3.00 | 1.76 | 6.00 | 3.53 | 4.00 | 2.35 |
| 5 | Polysorbate 80 | 2.00 | 1.18 | 2.00 | 1.18 | 2.00 | 1.18 |
| 6 | Purified water | q.s | - | q.s | - | q.s | - |
| 7 | Sodium Starch Glycolate | 6.00 | 3.53 | 6.00 | 3.53 | 6.00 | 3.53 |
| 8 | Magnesium stearate | 1.00 | 0.59 | 1.00 | 0.59 | 1.00 | 0.59 |
| **Total** | | 170.0 | 100.0 | 170.0 | 100.0 | 170.0 | 100.0 |

**Drug content of Glimepiride**

**Standard Preparation:** Glimepiride working standard equivalent to 60 mg were taken in to100ml volumetric flask and it was diluted with Methanol and acetonitrile and mixed. 5 ml was transferred in to 100ml volumetric flask and to this 10 ml of water was added. The volume was diluted with methanol and acetonitrile mixture in 50:50 ratios and was mixed.

**Test Preparation:** Ten tablets of bilayer formulation, containing Glimepiride were crushed into a fine powder by pestle in a mortar and the whole amount was taken in to a 100ml volumetric flask. 10 ml of water was added to it and sonicated for 3 minutes. 50 ml mixture of methanol and acetonitrile in 50:50 ratios were added with 15 minutes sonication followed by shaking in between, centrifugation at 3000rpm for 10 minutes were carried out. The volume was made adding the methanol and acetonitrile mixture

## Results and discussion

Both immediate release and extended release formulation are prepared and contain in a single dosage form. The study describes the formulation of both immediate and extended release drug for increased therapeutic efficacy and patient convenience. The bilayer tablets were prepared by wet granulation techniques using purified water and IPA as a solvent which has been tried many times for the good release behavior by taking various polymers. Suitable formulation has been optimized. In the present study an effort has been made to evaluate the drug content in the formulations against the claim kinetic study. It has been observed that the formulation possess linear release as compare to marketed layered tablet. During preformulation it has been observed that there is no drug-drug and drug excipient interaction, so the excipients which have been selected for the formulation are compatible with the drugs.

## Conclusion

This system provides zero order or near zero order release. This concept also demonstrates a wide technology for various applications such as instant release/slow release from one dosage form, because It allows the precise modulation of drug release process even for drug characteristics by extreme physicochemical properties.

## Acknowledgment

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## References

1) Dills D.G. and Schneider J. (1996). Clinical Evaluation of Glimepiride versus Glyburide in Type 2 Diabetes in a Double-blind Comparative Study, *Horm Metab Res*, **28**: 426–429.
2) Cox S.L. (2004). *Diabetes Today*, 40: 633-643.
3) Chein C.M. and Chou J. (2001). Matrix core of a modified release formulation, US Patent 6284275.
4) Kesarwani T., Kumar A. and Chawla M. (2005). Pharmaceutical compositions, World Intellectual patent organization.

**Table 3: Composition of Metformin SR tablets 500mg**

| S/N | B.No | F-IV | | F-V | | F-VI | | F-VII | | F-VIII | | F-IX | | F-X | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Without polymer | | With 10% of PEO | | With 20% of PEO | | With 30% of PEO | | With 10% of HPMC | | With 20% of HPMC | | With 30% of HPMC | |
| | Granulation | mg/Tab | %w/w | mg/Tab | %w/w | mg/Tab | %w/w | mg/Tab | %w/w | mg/Tab | %w/w | mg/Tab | %w/w | mg/Tab | %w/w |
| 1 | Metformin HCl | 502.46 | 46.96 | 502.46 | 46.96 | 502.46 | 46.96 | 502.46 | 46.96 | 502.46 | 46.96 | 502.46 | 46.96 | 502.46 | 46.96 |
| 2 | MCC (Avicel pH 101) | 465.54 | 43.51 | 358.54 | 33.51 | 251.54 | 23.51 | 144.54 | 13.51 | 358.54 | 33.51 | 251.54 | 23.51 | 144.54 | 13.51 |
| 3 | Povidone (Kollidon K90) | 18.00 | 1.68 | 18.00 | 1.68 | 18.00 | 1.68 | 18.00 | 1.68 | 18.00 | 1.68 | 18.00 | 1.68 | 18.00 | 1.68 |
| 4 | Povidone (Kollidon K90) | 27.00 | 2.52 | 27.00 | 2.52 | 27.00 | 2.52 | 27.00 | 2.52 | 27.00 | 2.52 | 27.00 | 2.52 | 27.00 | 2.52 |
| 5 | Purified water | q.s | - | q.s | - | q.s | - | q.s | - | q.s | - | q.s | - | q.s | - |
| 6 | Polyox WSR 301 | - | - | 53.50 | 5.00 | 53.50 | 5.00 | 107.00 | 10.00 | - | - | - | - | - | - |
| 7 | Polyox WSR N80 | - | - | 53.50 | 5.00 | 160.50 | 15.00 | 214.00 | 20.00 | - | - | - | - | - | - |
| 8 | HPMC K100 M | - | - | - | - | - | - | - | - | 107.00 | 10.00 | 214.00 | 20.00 | 321.00 | 30.00 |
| 9 | MCC Avicel (PH102) | - | - | - | - | - | - | - | - | 50.00 | 4.67 | 50.00 | 4.67 | 50.00 | 4.67 |
| 10 | Sodium CMC | 50.00 | 4.67 | 50.00 | 4.67 | 50.00 | 4.67 | 50.00 | 4.67 | - | - | - | - | - | - |
| 11 | Magnesium stearate | 7.00 | 0.65 | 7.00 | 0.65 | 7.00 | 0.65 | 7.00 | 0.65 | 7.00 | 0.65 | 7.00 | 0.65 | 7.00 | 0.65 |
| **Total** | | 1070.00 | 100.00 | 1070.00 | 100.00 | 1070.00 | 100.00 | 1070.00 | 100.00 | 1070.00 | 100.00 | 1070.00 | 100.00 | 1070.00 | 100.00 |

**Table 4: Physical parameters of Metformin SR and Glimepiride IR bilayer Tablets 1/500mg**

| Batch No. | Average Weight g (±SD) | Thickness mm (±SD) | Hardness KP (±SD) | Friability % (±SD) | Drug content %(±RSD) |
|---|---|---|---|---|---|
| Formulation F-I | 1239 (0.006) | 6.10 (0.008) | 11.43 (0.29) | 1.01 (0.51) | 98.36 (3.40) |
| Formulation F-II | 1236 (0.004) | 6.80 (0.006) | 12.76 (0.11) | 0.55 (0.02) | 97.56 (2.78) |
| Formulation F-III | 1242 (0.003) | 6.15 (0.009) | 13.21 (0.15) | 0.31 (0.09) | 96.98 (3.23) |
| Formulation F-IV | 1237 (0.002) | 6.15 (0.006) | 13.56 (0.20) | 0.39 (0.11) | 99.32 (2.03) |
| Formulation F-V | 1142 (0.005) | 6.20 (0.007) | 14.12 (0.19) | 0.41 (0.21) | 101.29 (2.75) |
| Formulation F-VI | 1139 (0.003) | 6.20 (0.011) | 13.85 (0.26) | 0.38 (0.12) | 100.32 (3.12) |
| Formulation F-VII | 1143 (0.002) | 6.15 (0.012) | 12.62 (0.21) | 0.39 (0.13) | 98.67 (2.54) |
| Formulation F-VIII | 1139 (0.001) | 6.20 (0.008) | 13.43 (0.15) | 0.37 (0.16) | 99.96 (2.56) |
| Formulation F-IX | 1140 (0.002) | 6.15 (0.006) | 12.78 (0.12) | 0.35 (0.18) | 100.03 (2.31) |
| Formulation F-X | 1139 (0.001) | 6.15 (0.005) | 13.42 (0.10) | 0.36 (0.14) | 99.7 (2.46) |