Research Article

Design and Development of Bilayer Tablets of Metformin Hydrochloride Sustained Release and Glimepiride Immediate Release for the Treatment of Type 2 Diabetes Mellitus

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Abstract

The primary objective of this study was to formulate bilayer tablets of metformin hydrochloride (sustained release) and glimepiride (immediate release) in which the dose of metformin was 500 mg and the dose of glimepiride was 1 mg and 2 mg. The tablets were prepared by wet granulation. In this study, glimepiride layer was formulated in the form of immediate release as an initial dose and metformin layer was in the form of sustained release to act as maintenance dose. The sustained release layer of metformin was prepared by using HPMC K100 M polymer. The prepared tablets were evaluated for various physicochemical parameters such as drug-excipient interaction by FTIR, flow properties, hardness, weight variation, thickness, friability, disintegration time for glimepiride layer, in vitro dissolution studies, assay and uniformity of content. The formulated tablets were found to be similar in drug release profile to that of market sample. These tablets were also subjected for real time and accelerated stability studies as per ICH guidelines. These tablets were found to be stable even after 6 months of stability study as all the parameters were within limit as per the specifications.

Keywords: Diabetes; Metformin Hydrochloride; Glimepiride; Bilayer tablets; Sustained release; Antidiabetic; HPMC K100 M

Introduction

Bilayer tablet is suitable for sequential release of two drugs in combination. Here, the glimepiride layer is formulated to obtain immediate release of drug, with the aim of reaching a high serum concentration in a short period of time. The metformin layer is in the form of sustained release which is designed to maintain an effective plasma level for a prolonged period of time. The pharmacokinetic advantage relies on the fact that drug release from fast releasing layer leads to a sudden rise in blood concentration. However, the blood level is maintained at steady state as the drug is released from the matrix of the sustained release layer. The bilayer tablets of metformin and glimepiride is used, with diet and physical exercise to treat type 2 diabetes mellitus. This combination product is used in case the use of glimepiride or metformin alone does not control blood glucose level.

Materials and Methods

The following raw materials were used for preparing bilayer tablets of metformin hydrochloride and glimepiride by wet granulation technique in which metformin was in layer 1 and glimepiride was in layer 2. This was a unique formulation in which metformin was in sustained release form and glimepiride was in immediate release form. Two different optimized batches were prepared in which the strength of metformin was 500 mg in each case whereas the strength of glimepiride was 1 mg and 2 mg respectively.

Sieving, Mixing, Granulation and Lubrication of Layer 1

Metformin Hydrochloride and HPMC K 100 M were sieved through 40 mesh (#40). Metformin Hydrochloride and first part of HPMC K 100 M were mixed at slow speed in RMG for 5 minutes. PVP K30 was dissolved in water and used as a granulating solution. Granulation was done in RMG with the help of granulating solution until desired granulation was achieved. The wet granules were passed through 16 mesh (#16) and dried in FBD with inlet temperature of 550C until the moisture content was below 3%. The dried granules were passed through 20 mesh (#20) and second part of HPMC K 100 M was mixed with it in RMG for 5 minutes. Magnesium Stearate was sieved through 60 mesh (#60) and used for lubrication. Lubrication was done in RMG for 45 seconds.

Sieving, Mixing, Granulation and Lubrication of Layer 2

Glimepiride was geometrically diluted with lactose and sieved through 40 mesh (#40). MCC PH 101 and first part of Crospovidone were also sieved through 40 mesh (#40). All the ingredients were mixed in RMG at slow speed for 5 minutes.

Table 1: *Raw materials, specification, quantity and their uses in tablets.*

S.No.	Raw Materials	Quantity (mg/tablet) F1	Quantity (mg/tablet) F2	Uses
	Layer 1			
1	Metformin HCl	500	500	Active
2	HPMC K100 M	90	90	Polymer
3	PVP K30	10	10	Binder
4	HPMC K100 M	90	90	Polymer
5	Magnesium Stearate	10	10	Lubricant
6	Purified Water	Q.S	Q.S	Solvent
	Weight of layer 1	**700**	**700**	
	Layer 2			
1	Glimepiride	1	2	Active
2	Lactose Monohydrate	90	90	Diluent
3	MCC PH 101	93.4	92.4	Diluent
4	Crospovidone	6	6	Disintegrant
5	PVP K30	2	2	Binder
6	Iron Oxide Red	0.1	0.1	Colour
7	Crospovidone	6	6	Disintegrant
8	Magnesium Stearate	1.5	1.5	Lubricant
9	Purified Water	Q.S	Q.S	Solvent
	Weight of layer 2	**200**	**200**	
	Total weight of tablet	**900**	**900**	

PVP K30 and Iron Oxide Red were dissolved in water and used as granulating solution. Granulation was done in RMG with the help of granulating solution until desired granulation was achieved. The wet granules were passed through 16 mesh (#16) and dried in FBD with inlet temperature of 550C until the moisture content was below 3%. The dried granules were passed through 20 mesh (#20) and second part of Crospovidone was mixed with it in RMG for 5 minutes. Magnesium Stearate was sieved through 60 mesh (#60) and used for lubrication. Lubrication was done in RMG for 45 seconds.

The moisture content of the lubricated granules was observed in Denever digital moisture analyzer at 105°C. The angle of repose (Θ) was also performed for the lubricated granules and was found to be less than 30° and hence it reveals good flow property. The pre-compression parameters of the bulk lubricated powder were performed using Electrolab Tapped Density Tester USP.

Table 2: *Moisture content and Angle of Repose.*

S.No.	Experiment	Result (F1)		Result (F2)	
		Layer 1	Layer 2	Layer 1	Layer 2
1.	Moisture Content (Lubricated Granules)	3.16%	2.85%	3.22%	3.06%
2.	Angle of Repose (Θ)	27°24'	26°18'	28°12'	26°22'

Table 3: *Pre-compression parameters of bulk lubricated powder.*

S.No.	Experiment	Result (F1)		Result (F2)	
		Layer 1	Layer 2	Layer 1	Layer 2
1.	Bulk Density	0.48 g/cc	0.52 g/cc	0.47 g/cc	0.53 g/cc
2.	Tapped Density	0.57 g/cc	0.60 g/cc	0.55 g/cc	0.60 g/cc
3.	Carr's Index	15.79%	13.33%	14.55%	11.67%
4.	Hausner's Ratio	1.19	1.15	1.17	1.13

Compression
After performing the pre-compression parameters, the lubricated powder was subjected for compression using Karnavati 9 station double rotary tablet punching machine. The punching tools used were oblong, biconvex, 19.5 x 9.0 mm plain on both sides. The machine RPM was 15. The average punch weight of the tablets was 900mg in which the average weight of layer 1 was maintained as 700 mg and average weight of layer 2 was maintained as 200 mg. The hardness, thickness, weight variation and friability of the punched tablets were maintained in the desired range.

Hardness
Tablets require a certain amount of strength or hardness to withstand mechanical shocks of handling in manufacturing, packing and shipping. The hardness of the tablets was maintained between 90 to 120 Newton. Hardness was measured using digital Campbell Electronics tablet hardness tester.

Thickness
The thickness of tablets should be maintained to overcome packing problems. The thickness of punched tablets was maintained in the range of 6.2 to 6.6 mm with the average thickness of 6.3 mm. Thickness was measured using Dial Vernier Caliper.

Weight Variation
The average percentage weight variation was within ±7.5% i.e. in the pharmacopoeia limit.

Friability
The friability test was performed using Electrolab Tablet Friability Tester. This is important to know the mechanical strength of tablets while handling. The friability of the punched tablets was found to be 0.19% (F1) and 0.22% (F2).

Disintegration
Disintegration time of the punched tablets (layer 2 consisting of Glimepiride) was done using Veego Disintegration Test Apparatus. One tablet was placed in each of the 6 tubes of the basket and disintegration was carried out using water maintained at 37°±2°C. The time taken for complete disintegration of the Glimepiride layer of tablets with no palpable mass remaining in the apparatus was measured and recorded. The minimum disintegration time was 50 seconds and the maximum disintegration time was 1 minute 45 seconds for these tablets. The
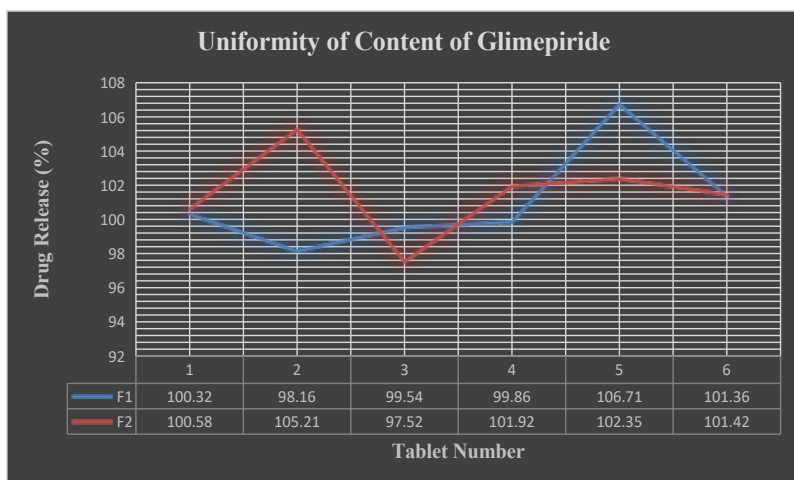
average disintegration time was 1 minute 25 seconds (F1) and 1 minute 45 seconds (F2).

Table 4: Summary of Post-compression parameters.

S.No.	Test	Result (F1)	Result (F2)
1.	Hardness	96 to 110 Newton	96 to 110 Newton
2.	Thickness	6.3 mm average thickness	6.3 mm average thickness
3.	Weight Variation	Between 849 to 932 mg	Between 851 to 940 mg
4.	Friability	0.19%	0.22%
5.	Disintegration	1 minute 25 seconds on average	1 minute 45 seconds on average
6.	Dissolution (Glimepiride)	92.00 to 101.0%	89.00 to 103.0%
7.	Assay (Glimepiride)	100.13%	101.22%
8.	Assay (Metformin HCl)	100.56%	100.48%
9.	Uniformity of Content (Glimepiride)	98.16 to 106.71%	97.52 to 105.21%
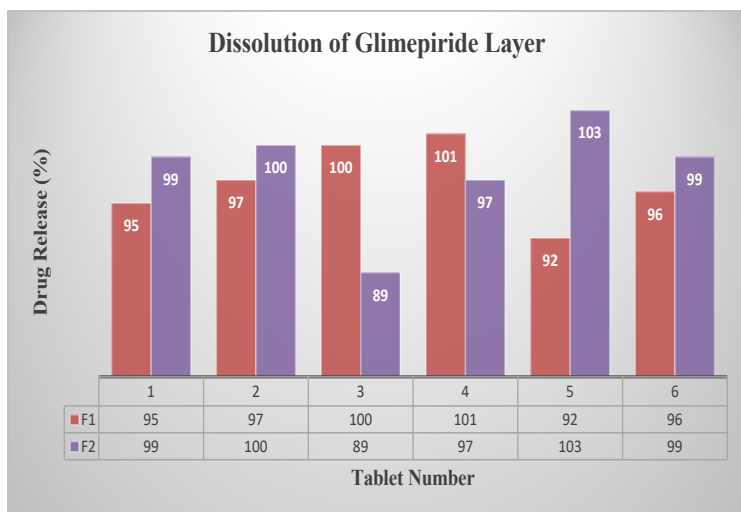
Graph 1: *Dissolution of Glimepiride Layer (F1 and F2).*

	1	2	3	4	5	6
F1	95	97	100	101	92	96
F2	99	100	89	97	103	99

Graph 2: *Uniformity of Content of Glimepiride (F1 & F2).*

	1	2	3	4	5	6
F1	100.32	98.16	99.54	99.86	106.71	101.36
F2	100.58	105.21	97.52	101.92	102.35	101.42

Method of Analysis

Identification of Glimepiride:

In the assay, the principal peak in the chromatogram obtained with the sample solution corresponds to the peak in the chromatogram obtained with the standard Glimepiride RS solution.

Identification of Metformin HCl:

The light absorption spectrum of the sample in the range from 210 nm to 310 nm should correspond to be with the absorption spectrum of working standard in the assay.

Dissolution of Glimepiride:

Dissolution parameters
Medium: 900 ml phosphate buffer pH 7.8
Apparatus: Paddle
Temperature: 37±0.5°C
Revolution: 100 RPM
Time: 45 minutes

Preparation of 1000 ml Phosphate buffer pH 7.8

Dissolve 0.58 gram of monobasic potassium phosphate and 8.86 gram of anhydrous dibasic sodium phosphate in 1000 ml water. Adjust the pH to 7.8 with dilute phosphoric acid or 1 M sodium hydroxide.

Standard Preparation:

Weigh accurately 25 mg Glimepiride WS in 200 ml volumetric flask and dissolve it with 100 ml of 90% acetonitrile by sonicating for 5 minutes. Allow to cool at room temperature & make up the volume with same. Dilute 2 ml of this solution to 200 ml with dissolution medium. Further dilute 10 ml of this solution to 25 ml with 50% methanol & filter through 0.2 micron filter paper.

Sample Preparation:

Place 1 tablet in each dissolution jar and run the apparatus as per above dissolution parameters. Collect 15 ml of sample from each vessel at specified time interval and filter. Dilute 10 ml of this filtered solution to 25 ml with 50% methanol & filter through 0.2 micron-filter paper.

Procedure:

Proceed as prescribed in the assay method using 50µl injection volume and calculate the dissolution in percent of each tablet with respect to claim amount using the formula.

Calculation:

$$\frac{\text{Area of Sample}}{\text{Area of Standard}} \times \frac{\text{Wt. of Standard (g)}}{0.001} \times \frac{9}{200} \times \frac{100\text{-Water \%}}{\text{Potency \% WS}} \times \text{Average wt. (mg/tab)} \times \frac{x}{100}$$

Result: Glimepiride %

Uniformity of content Glmepiride:

Sample preparation: weigh 10 tablets individually and place one tablet in each of 10 in 100 ml volumetric flask, add about 70 ml of 90% acetonitrile. Shake well and sonicate for about 20 minutes. Cool at room temperature and make up the volume to mark with same solvent. Centrifuge if necessary and filter the solution through 0.2 micron filter paper.

Standard Preparation: Weigh about 25 mg of glimepiride

working standard in 100 ml volumetric flask, add about 70 ml of 90% acetonitrile and sonicate for about 5 minutes. Cool to room temperature and make up the volume to mark with same solvent. Dilute 2ml to50 ml with same solvent and filter through 0.2 μm filter paper.

Procedure: Proceed as prescribed in assay method, using 10μl injection volume.

Calculation:

$$\frac{\text{Area of Sample}}{\text{Area of Standard}} \times \frac{\text{Wt. of Standard (g)}}{\text{Avg. Assay (g)}} \times \frac{2}{50} \times \frac{100\text{-Water \%}}{100} \times \text{Potency \% WS}$$

Result: Glimepiride %

Assay
Glimepiride:
Instrumentation and requirements
1.Chromatograph:

Pump   Shimadzu XR gradient system with two pumps

Detector   Shimadzu XR with semi micro flow cell

Column   Octadecylsilane, 2.6 micron particle size, Dimension 150 x 4.6 mm (sunshell)

Injection   Shimadzu XR Auto sampler

Column Oven   Shimadzu XR

2.Chromatography Conditions:

Temperature   35°C
Detection   228nm
Run time   10 min
Flow rate   1.0ml/min
Injection Volume   10μl

3.Mobile Phase

Weigh accurately 250 g of NaH_2PO_4 and dissolve in 250 ml HPLC water, and adjust pH to 2.5 with Phosphoric acid (10%). Mix with 250 ml HPLC grade acetonitrile and sonicate for 10 minutes. Cool to room temperature and filter the solution through 0.2 μm filter paper using vacuum pressure.

Method of Analysis
Standard Preparation:
1.Glimepiride WS:
Weigh accurately 25mg of Glimepiride working standard and transfer in 100 ml volumetric flask. Add about 70 ml of 90% acetonitrile and sonicate for 5 minutes, cool to room temperature, make up the volume to 100 ml with same solvent. Further dilute 2ml of this solution to 50 ml with same solvent and filter through 0.2μm filter paper.

2.Sample Preparation:
Weigh 20 tablets and find the average weight per tablet. Crush the 20 tablets and mix homogeneously with the help of mortar and pestle. Weigh accurately tablet powder equivalent to 1mg Glimepiride and transfer in 100 ml volumetric flask. Add 70 ml of 90% acetonitrile and sonicate for about 20 minutes. Allow to cool at room temperature and make up the volume to mark with same solvent. Centrifuge the solution for 5 minutes and filter through 0.2μm filter paper.

3. Procedure:
Separately inject 10μl of standard preparation and the sample preparation into the injection valve and note the chromatographic area for quantification.

System suitability:
A. Glimepiride:
In the chromatogram obtained from the standard preparation,

the column efficiency determined from the major peak is not less than 1000 theoretical plate, the tailing factor is not more than 2.0 and the relative standard deviation of replicate injections is not more than 2.0%.

Calculation:
Glimepiride:

$$\frac{\text{Area of Sample}}{\text{Area of Standard}} \times \frac{\text{Wt. of Standard (g)}}{\text{Wt. of Sample (g)}} \times \frac{2}{50} \times \frac{100\text{-Water \%}}{100} \times \frac{\text{Potency \% WS}}{100} \times \text{Average weight (mg/tab)}$$

Dissolution:
Metformin HCl
1   Dissolution Parameter:
2   Medium: 1000 ml Phosphate buffer pH 6.8
3   Apparatus: Paddle
4   Revolution: 100 RPM
5   Temperature: 37 ± 0.5°C
6   Time: 1 hour, 3 hours and 10 hours

Phosphate buffer pH 6.8:
Dissolve 6.8 g of monobasic potassium phosphate in 500 ml water. Add 112 ml 0.2N Sodium hydroxide solution and then dilute to 1000 ml with water. Adjust the pH to 6.8 with 0.2 N NaOH if necessary.

5.2.1 Standard Preparation:
Weigh accurately 50 mg of Metformin HCl WS in 250 ml volumetric flask. Dissolve it in about 200 ml of dissolution medium and make up the volume with same medium. Dilute 5 ml of this solution to 100 ml with the dissolution medium.

Procedure:
Place one tablet in each dissolution vessel with help of suitable sinker and run the apparatus as per   above dissolution parameters. Withdraw 10 ml of sample from each dissolution vessel at specified time interval and filter. Replenish each vessel with 10 ml of dissolution media after each sampling. Measure the absorbance of the sample and standard solution in UV-Vis spectrophotometer at about 232 nm and calculate the result by comparison method.

Calculation:
Calculate the dissolution in percent of each tablet at required time interval with respect to claimed amount using the below formula.

First Hour:
Sample dilution: 2 ml to 50 ml with dissolution media

$$\frac{\text{Abs of Sample}}{\text{Abs of Standard}} \times \frac{\text{Wt. of Std (mg)}}{250} \times \frac{5}{100} \times \frac{1000}{\text{Claim (mg)}} \times \frac{50}{2} \times \frac{100\text{-Water \%}}{100} \times \text{Potency \% WS}$$

Third Hour:
Sample dilution: 2 ml to 100 ml with dissolution media

$$\left\{ \frac{\text{Abs of Spl}}{\text{Abs of Std}} \times \frac{\text{Wt.of Std (mg)}}{250} \times \frac{5}{100} \times \frac{1000}{100} \times \frac{100}{2} \times \frac{100\text{-Water \%}}{100} \times \text{Potency \% WS} + A \right\} \times 100 \div \text{claim in mg}$$

Tenth Hour:
Sample dilution: 2 ml to 100 ml with dissolution media

$$\left\{ \frac{\text{Abs of Spl}}{\text{Abs of Std}} \times \frac{\text{Wt.of Std (mg)}}{250} \times \frac{5}{100} \times \frac{1000}{100} \times \frac{100}{2} \times \frac{100\text{-Water \%}}{100} \times \text{Potency \% WS} + A+B \right\} \times 100 \div \text{claim in mg}$$

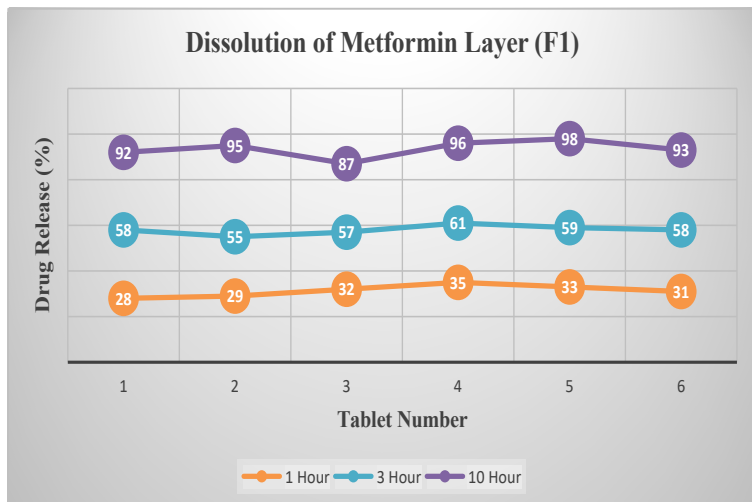**Results:** Metformin HCl %
Where,
A- Amount of Metformin HCl (mg) sample during first hour
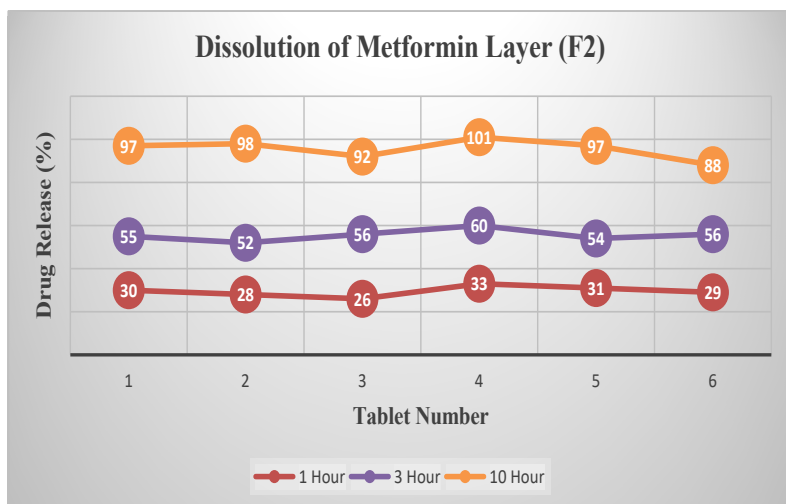
analysis

B-Amount of Metformin HCl (mg) sample during third hour analysis

Table 5: Summary of Dissolution (Metformin Layer).

S.No.	Dissolution Time	Result (F1)	Result (F2)
1.	1 Hour	28 – 35%	26 – 33%
2.	3 Hour	55 – 61%	52 – 60%
3.	10 Hour	87 – 98%	88 – 101%

Graph 3: *Dissolution of Metformin Layer (F1).*

Graph 4: *Dissolution of Metformin Layer (F2).*

Assay:

1. Metformin HCl:
2. Instrumentation and requirements
3. Instrument: UV-Visible spectrometer
4. Diluents: Water
5. Conditions
       Temperature: Ambient
       Detection: 232 nm

6. Standard Preparation:

Weigh accurately about 50 mg of metformin HCl WS in 250 ml volumetric flask. Add 200 ml of diluent and shake for few min-utes and sonicate for 25 minutes. Cool, make up the volume to mark with same diluent. Dilute 5 ml of this solution to 100 ml with same diluent.

7. Sample Preparation:

Weigh 20 tables and find the average weight per tablet. Crush 20 tablets and mix homogeneously with the help of mortar and pestle. Weigh accurately tablet powder equivalent to 50 mg of Metformin HCl and transfer in 250 ml volumetric flask. Add 200 ml of diluent; shake for few minutes and sonicate for 25 minutes for complete dissolution; cool the solution to room

$$\frac{\text{Area of Sample}}{\text{Area of Standard}} \times \frac{\text{Wt. of Std (g)}}{\text{Wt. of Spl (g)}} \times \frac{2}{50} \times \frac{100 - \text{Water \%}}{100} \times \frac{\text{Potency \% WS}}{100} \times \text{Avg. wt. (mg/tab)}$$

temperature ad make up the volume with same diluent. Sediment or centrifuge the solution at 2000 RPM for 10 minutes. Dilute 5 ml of this solution o 100 ml with same diluent.

8. Procedure:

Measure the absorbance of both standard and sample solution at maximum at about 232 nm and calculate the results by comparison.

9. Calculation:

Metformin HCl

Result: Metformin HCl %

Packing: The primary packing of these tablets was done in clear PVDC blister. 10 tablets were packed in each blister.

Stability Studies: After blister packing, these tablets were subjected for real time and accelerated stability studies as per ICH guidelines for 6 months. The real time stability was carried out by storing the tablets at 30°C ± 2°C and 75% ± 5% RH. The accelerated stability was carried out by storing the tablets at 40°C ± 2°C and 75% ± 5% RH in Thermolab Stability chambers.

Conclusion

Bilayer tablets of Metformin Hydrochloride Sustained release and Glimepiride immediate release were successfully formulated by employing wet granulation method. HPMC K 100 M was used as sustained release polymer in Metformin Hydrochloride layer and crospovidone was used as superdisintegrant in Glimepiride layer. Pre-compression parameters such as bulk density, tapped density, Carr's Index, Hausner's ratio and angle of repose was done for the bulk lubricated granules and this revealed good flow and compressibility property of the bulk granules. Post-compression parameters such as hardness, thickness, weight variation, friability, disintegration (for glimepiride layer only), dissolution, assay and uniformity of content (for glimepiride) was performed on punched tablets and all the parameters was found to comply with the in-house specification. Real and accelerated stability study was carried out for a period of 6 months as per ICH guidelines and the formulation was examined for physical appearance, average weight, disintegration time, hardness, assay and dissolution. All the tests showed satisfactory results according to in house specifications.

Table 4.1: Summary of stability report.

Duration (months)	Storage condition	Colour (F1 & F2)	Average weight (mg)		Glimepiride DT (minute)		Hardness (N)	
			F1	F2	F1	F2	F1	F2
1	Real	Metformin Layer - White Glimepiride Layer - Pink	902	899	1.10	1.30	98 - 105	97 - 108
1	Accelerated	Metformin Layer - White Glimepiride Layer - Pink	900	901	1.20	1.40	97 - 106	99 - 109
3	Real	Metformin Layer - White Glimepiride Layer - Pink	905	900	1.25	1.20	96 - 108	95 - 110
3	Accelerated	Metformin Layer - White Glimepiride Layer - Pink	901	904	1.50	1.75	97 - 103	94 - 106
6	Real	Metformin Layer - White Glimepiride Layer - Pink	896	902	1.35	1.45	98 - 106	95 - 108
6	Accelerated	Metformin Layer - White Glimepiride Layer - Pink	908	889	1.50	1.35	96 - 109	97 - 107

Table 4.2: Summary of stability report.

Duration (months)	Storage condition	Glimepiride Assay (%)		Metformin Assay (%)	
		F1	F2	F1	F2
1	Real	101.60	101.56	100.54	100.61
1	Accelerated	101.38	101.48	100.21	100.25
3	Real	101.25	101.14	100.30	100.34
3	Accelerated	100.12	100.62	100.60	100.46
6	Real	100.06	100.15	100.51	100.38
6	Accelerated	99.33	100.20	100.26	100.60

Table 4.3: Summary of stability report.

Duration (months)	Storage condition	Glimepiride Dissolution (%)		Metformin Dissolution (%)	
		F1	F2	F1	F2
1	Real	92 to 101	90 to 102	1Hour: 27 to 35 3 Hour: 55 to 62 10 Hour: 88 to 99	1Hour: 26 to 34 3 Hour: 52 to 61 10 Hour: 87 to 101
1	Accelerated	88 to 102	89 to 103	1Hour: 25 to 35 3 Hour: 54 to 60 10 Hour: 86 to 98	1Hour: 27 to 35 3 Hour: 54 to 62 10 Hour: 88 to 100
3	Real	90 to 101	91 to 102	1Hour: 25 to 33 3 Hour: 55 to 62 10 Hour: 87 to 100	1Hour: 25 to 35 3 Hour: 53 to 60 10 Hour: 90 to 101
3	Accelerated	92 to 101	90 to 100	1Hour: 28 to 35 3 Hour: 55 to 61 10 Hour: 87 to 99	1Hour: 26 to 33 3 Hour: 52 to 60 10 Hour: 88 to 99
6	Real	91 to 102	94 to 101	1Hour: 30 to 36 3 Hour: 53 to 60 10 Hour: 89 to 100	1Hour: 24 to 34 3 Hour: 50 to 59 10 Hour: 88 to 100
6	Accelerated	87 to 101	88 to 100	1Hour: 29 to 35 3 Hour: 51 to 62 10 Hour: 87 to 99	1Hour: 25 to 34 3 Hour: 55 to 60 10 Hour: 89 to 100

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