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FORMULATION AND EVALUATION OF METFORMIN AND GLIMEPIRIDE BILAYERED TABLET

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ABSTRACT

The aim of the present study was to establish bilayer tablet formulation containing Metformin hydrochloride as sustained release layer and Glimepiride as conventional immediate release layer. Layer containing Metformin hydrochloride 1 g exhibits sustained release, were prepared by wet granulation method using hydroxypropylmethyl cellulose K15 M and K4 M as matrix forming polymers and Poly-vinyl-pyrrolidone K-30 as binder along with isopropyl-alcohol as binding liquid. Immediate release layer containing Glimepiride were prepared by wet granulation method using poly-vinyl-pyrrolidone as binder with water. Crosscarmellose sodium used as intra granular as well as extragranular superdisintegrant in immediate release layer. Colour erythrosine lake was used to differentiate layers and to enhance elegance of the tablets. The prepared granules were evaluated for bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose, the concentrations of on mechanical additives i.e. glidants and lubricants are efficient enough to keep the values of these parameters within very good to excellent level as per USP. In vitro release studies were carried out by USP type 1 apparatus (Basket) for SR layer and USP type 2 apparatus (Paddle) for IR layer. The results showed that hydroxypropylmethyl cellulose K15M in sustained layer can control the release of drug. The in vitro release profile of drug from sustained release layer diffusion was the dominant mechanism of drug release. The formulation (GF5) having immediate release layer produces immediate effect 97 $\pm$ 0.24% within 15 minutes. The formulation (MF8) having Sustained release layer produces sustained release effect 98 $\pm$ 0.41 % up to 12 hours.

KEYWORDS: Bilayer tablet, Glimepiride, Metformin HCl, Sustained Release.

INTRODUCTION

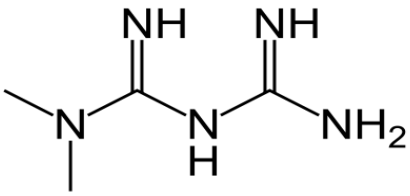

Figure 1: Metformin Hydrochloride.

N,N-Dimethylimidodicarbonimidic diamide

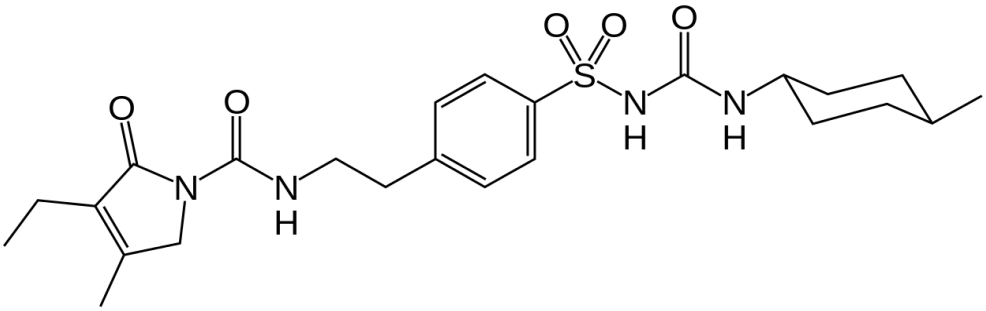

Figure 2: Glimepiride.

3-ethyl-4-methyl-*N*-(4-[*N*-((1*r*,4*r*)-4-methylcyclohexylcarbamoyl)sulfamoyl]phenethyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxamide

Tablets [1,4]

Pharmaceutical tablets are the oldest and more popular unit dosage forms. Tablets are easy to administer, easy to dispense, cost effective and easy to manufacture. Dual release tablet is a unit compressed tablet dosage form that contains two parts in which one part having conventional or immediate release and another one is sustained or controlled release.

Multilayered tablets

Multilayered tablet consists of two or more layers of granules or powder compressed together. This dosage form has the advantage of separating two incompatible substances in a single unit dosage form. It comprises several different granules that are compressed to form a single tablet composed of two or more layers and usually each layer is essentially of different colour to be distinctive within a single unit tablet.

Literature Review

Asha Patel et al. developed controlled release floating drug delivery system of Metformin HCl microspheres by non-aqueous emulsification solvent evaporation technique using

ethylcellulose as the rate controlling polymer and 250 mg of Metformin hydrochloride. The experimental design supported product development and optimization procedure yielded the desired microspheres with drug release equivalent to those of the marketed single unit dosage forms with the added advantage of floatability in gastric juice for prolonged slow release.

Uttam Mandal et al. designed an oral sustained release sustained matrix tablet of Metformin HCl and optimizes the drug profile using response surface methodology. The tablets were formulated by non aqueous wet granulation method using HPMC K 15M as matrix forming polymer. HPMC K15M and PVP were taken as the independent variables.

Subramaniam Kannan et al. Performed for the formulation and evaluation of sustained release tablets of Aceclofenac using hydrophilic matrix system to develop once daily sustained release tablets of Aceclofenac (200mg) by wet granulation using hydrophilic polymer like hydroxypropyl methyl cellulose K-100. The drug excipients mixtures were subjected to preformulation studies. The tablets were subjected to physicochemical studies, in-vitrodrug release, kinetic studies and stability studies.

Cananersoya et al. studied the effect of Metformin on markers of endothelial function, vascular inflammation and factors of thrombosis in obese type 2 diabetic patients. 24 type II diabetic patients (15 female and 9 male) which was previously under medical nutrition treatment (MNT) + regular exercise programme (REP) without chronic micro or macrovascular complications with the mean age of 50.5 ± 1.5 years, diabetes duration of 17.9 ± 6.3 months and body mass index (BMI) of 31.7 ± 0.8 kg/m2 were enrolled in the study.

MATERIALS AND METHODS

Drug-Excipient Compatibility Studies by FTIR Spectroscopy

Fourier-transform infrared (FTIR) spectra of the Drug and polymer were obtained on Alpha Brooker FTIR (Tokyo, Japan). In the present study, the potassium bromide dispersion micro disc sample holder method was employed. The spectra were scanned over the wave number range of 4000 cm-1to 400 cm-1.

Formulation Different batches

Table 1: Composition of formulations of Metformin SR layer.

Sr. No.	Ing.	MF1	MF2	MF3	MF4	MF5	MF6	MF7	MF8	MF9
DRY MIX										
1	Metformin HCl	1000	1000	1000	1000	1000	1000	1000	1000	1000
2	MCC PH 101	75	55	35	15	--	--	--	--	15
3	HPMC K 4 M	190	210	230	250	110	80	40	--	--
4	HPMC K15M	--	--	--	--	150	180	210	250	235
BINDER										
5	PVP K-30	15	10	10	10	15	15	25	25	25
6	IPA	10	10	10	10	10	10	10	10	10
LUBRICATION										
7	Mg. Str.	5	10	10	10	10	10	10	10	10
Weight of SR Part		1285	1285	1285	1285	1285	1285	1285	1285	1285

Table 2: Composition of formulations of Glimepride IR layer.

Sr. No.	Ing.	GF1	GF2	GF3	GF4	GF5	GF6	GF7
DRY MIX								
1	Glimepiride	2.000	2.000	2.000	2.000	2.000	2.000	2.000
2	MCCP	40.000	30.000	20.000	--	--	--	--
3	Lact. Mono.	20.000	30.000	40.000	60.000	60.000	60.000	65.000
4	CCS	8.000	8.000	8.000	8.000	10.000	5.000	5.000
BINDER								
5	PVP K-30	5.000	5.000	5.000	5.000	3.000	3.000	3.000
6	Pu.Water	6.000	6.000	6.000	6.000	6.000	6.000	6.000
LUBRICATION								
7	CCS	10.000	10.000	10.000	10.000	10.000	15.000	10.000
8	Mg. Str.	3.000	3.000	3.000	3.000	3.000	3.000	3.000
9	Lake Eryth.	0.200	0.200	0.200	0.200	0.200	0.200	0.200
Weight of IR Part		**94.200**	**94.200**	**94.200**	**94.200**	**94.200**	**94.200**	**94.200**

Combined Wt. = Wt. of SR part + Wt. of IR part

METHOD OF GRANULATION

1. **SR Part:** Formulations (MF1, MF2, MF3, MF4, MF5, MF6, MF7, MF8, and MF9) were prepared according to the Table 1. Metformin hydrochloride, Methocel K4M, Methocel K15M, Microcystalline cellulose were mixed uniformly in polybag and granulated with non aqueous solution of Kollidon K30 in Isopropyl alcohol followed by tray drying at 60˚C, the dried granules passed through #30 mesh and finally blended with magnesium stearate in appropriate quantities and compressed with 21.5 mm x 9.75 mm capsule shape standard concave punches with and/or without IR layer containing glimepiride.

2. **IR Part:** Formulations (GF1, GF2, GF3, GF4, GF5, GF6, and GF7) were prepared according to the Table 2. Glimepiride, Avicel (Microcrystalline cellulose plain), Lactose

monohydrate, Croscarmellose sodium were mixed uniformly in poly-bag and granulated with non aqueous solution of Kollidon K30 (Polyvinyl pyrrolidone K-30) in Isopropyl alcohol followed by tray drying at 60˚C, the dried granules were passed through #30 mesh and finally blended with magnesium stearate in appropriate quantities for not more than 5 minutes and compressed with 21.5 mm x 9.75 mm capsule shape standard concave punches alongwith metformin SR layers.

Characterisation of Granules

1. **Bulk density:** Calculated by taking 10 g of granules & 50 ml volume of tap density apparatus, calculated as weight of granules divided by bulk volume (Appearant volume without tapping)

$$\text{Bulk density} = \frac{\text{Weight}}{\text{Bulk volume}}$$

2. **Tapped density:** Calculated by taking 10 g of granules & 50 ml volume of tap density apparatus, calculated as weight of granules divided by tapped volume (Appearant volume after tapping : 100 tapings)

$$\text{Tapped density} = \frac{\text{Weight}}{\text{Tapped volume}}$$

3. **Housner's Ratio:** Calculated by taking 10 g of granules & 50 ml volume of tap density apparatus, calculated as tap density divided by bulk density.

$$\text{Housner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

4. **Carr's Index/Compressibility Index:** Calculated by taking 10 g of granules & 50 ml volume of tap density apparatus, calculated as tap density divided by bulk density.

$$\text{Compressibility Index} = \frac{\text{Tapped density - Bulk densiry}}{\text{Tapped density}} \times 100$$

5. **Angle of Repose**

$$\text{Angle of Repose} = \text{Tan}^{-1}\frac{\text{Height of heap}}{\text{Radius}}$$

6. **Drug Content**

Drug Content of tablet is determined HPLC method (Waters Acuity H class) using Inertsil ODS 250 mm x 4.6 mm x 5µm chromatographic column. And detection wavelength 235 nm.

COMPRESSION

Amongst above all formulations are subjected to compression, first SR part is compressed individually and characterized alone for dissolution study. And then IR layer is chosen for compression alongside most selected formulation since IR part could not be compressed alone in specified dimensions of punches. After successful development of both the formulations most suited formulas are chosen for compression together.

Characterisation of Compressed Tablets

Physical Characterization of Tablets

Formulated tablets after compessions were subjected to different physical characterization studies.

1. **Uniformity of weight:** The weight variation was determined on 20 tablets using an electronic balance (Electolab, India).
2. **Diameter:** Ten tablets were taken and their thickness was recorded by a digital Vernier calliper. (Martuyoko, Japan)
3. **Thickness:** Ten tablets were taken and their thickness was recorded by a digital Vernier calliper. (Martuyoko, Japan)
4. **Hardness:** Tablet hardness was determined for a minimum of six tablets using a vertically mounted Pfizer type hardness tester (Veego, India).
5. **Friability:** Friability was calculated as the percentage weight loss of 20 tablets using a Roche type friabilator (Electrolab India) for 4 min at 25 rpm.

Chemical Characterization of Tablets

1. **Drug Content of Tablets or Assay**

About 20 tablets were finely powdered, powdered sample equivalent to 1000 mg of Metformin hydrochloride was accurately weighed and transferred to a 200 mL volumetric flask, 100 ml mobile phase was added, sonicated for 30 minutes in water bath with temperature not exceeding 20°C. Final volume was made with mobile phase. Further, diluted 5 ml of above solution to 50 ml with mobile phase. Mobile phase used was Trifluroacetic acid 0.1 % previously adjusted to pH 2.92 with liquid ammonia solution 28 parts and methanol 72 Parts. Standard solutions were prepared in same manner (Glimepiride 1 ppm & Metformin hydrochloride 500 ppm). The drug content of the formulated tablets was estimated using HPLC system (Waters Acuity H Class), using Inertsil ODS 250 mm x 4.6 mm x 5µm chromatographic column. and detection wavelength 235 nm.

2. Content uniformity

10 tablets were taken at random and weighed accurately individual tablet, transferred to a 200 mL volumetric flask each, 100 ml mobile phase was added, sonicated for 30 minutes in water bath with temperature not exceeding 20°C. Final volume was made with mobile phase. Further, diluted 5 ml of above solution to 50 ml with mobile phase. Mobile phase used was Trifluroacetic acid 0.1 % previously adjusted to pH 2.92 with liquid ammonia solution 28 parts and methanol 72 Parts. Standard solutions were prepared in same manner (Glimepiride 1 ppm & Metformin hydrochloride 500 ppm). The drug content of the formulated tablets was estimated using HPLC system (Waters Acuity H Class), using Inertsil ODS 250 mm x 4.6 mm x 5µm chromatographic column. and detection wavelength 235 nm.

3. In-vitro Dissolution Study

a. SR Part

The in vitro dissolution studies were performed by USP type I (Basket) dissolution apparatus at 100 rpm. The dissolution medium consisted of 1000 ml phosphate buffer pH 6.8 was maintained at 37˚C ± 0.5˚C in each dissolution vessle. An aliquot (5 ml) was withdrawn at specific time intervals (1h, 2h, 4h, 8h & 12 h) and replaced with the same volume of fresh medium at same temperature. The withdrawan sample was filtered through 0.22 µm filter paper. Next, its drug content was determined by UV spectrophotometer (Schimadzu 1700) using wavelength 232 nm. The release studies were conducted in triplicate. Mean percent cumulative drug release was plotted against time of release.

b. IR Part

The in vitro dissolution studies were performed by USP type 2 (Paddle) dissolution apparatus at 75 rpm for 15 minutes (sampling intervals 5 min & 15 min). The dissolution medium consisted pH 7.8 phosphate buffer (0.58 g of monobasic potassium phosphate and 8.86 g of dibasic sodium phosphate anhydrous, in 1000 mL of water, adjust with 10% phosphoric acid or 1 N sodium hydroxide to a pH of 7.8 900 mL was maintained at 37˚C ± 0.5˚C. An aliquot (5 ml) was withdrawn at specific time intervals and replaced with the same volume of fresh medium at same temperature. The withdrawal sample was filtered through 0.22 µm filter paper. Next, its drug content was determined by HPLC (Waters Acuity H class) using chromatographic column 4.0-mm × 12.5 cm packing L1 at wavelength 228 nm. The release studies were conducted in triplicate. Mean percent cumulative drug release was plotted against time of release.

RESULTS AND DISCUSSION

In the present study, granules for SR part containing 1g Metformin hydrocloride were prepared initially using various compositions (Table 1) of matrix forming polymers (HPMC K15M, HPMC K4M) with the help of granulating agent i.e. Polyvinyl pyrrolidone K-30 with isopropyl alcohol.

Granules for IR part containing 2 mg glimepiride were prepared initially using various compositions (Table 2) using granulating agent i.e. Polyvinyl pyrrolidone K-30 with purified water. Croscarmellose sodium was used as intra as well as extra granular disintegrant.

Granules for SR part as well as for IR part are characterized for physical parameters Table 3.

Tablets were tested to check dissolution period up to 12 hrs for about 90-95 % cumulative drug release. Tablets with code no MF8 exhibited extended drug release up to 12 hr (Table 6 A). Rate of drug release was significant when HPMC K 15 M used as Matrix builder. HPMC K15M gave the effect of hydrophilic polymer leading to controlled and extended release of drug (Table 6 A, MF8). It seems that hydrophilic diffusion layer created by high viscosity cross linking polymer HPMC K15 M made the dissolution process almost diffusion controlled. Retardation of permeation by matrix formed by HPMC K15 M caused controlled and extended release of drug. Physical characteristics of these granules were recorded and tabulated in (Table 3 A & B). Physical characteristics of these tablets were recorded and tabulated in Table 4.

The sustained release of Metformin hydrochloride SR layer shown in Table 6 A (MF8) This indicated combined effect of diffusion and erosion mechanism on the release of drug. (Table 6 A MF8). Also the immediate release of Glimepiride IR layer shown in Table 6 B (GF5).

1. Characterisation of Lubricated Granules

Table 3 A: Characterisation of Granules of formulations of Metformin SR layer.

Formulation Code	Bulk Density	Tapped Density	Hausner's ratio	Carr's Index	Angle of repose (θ)	Drug Content
MF1	0.429±0.04	0.579±0.04	25.91±0.04	0.74	30.19°	98.89±0.34
MF2	0.433±0.04	0.583±0.04	25.73±0.04	0.74	29.24°	99.23±0.84
MF3	0.432±0.04	0.582±0.04	25.77±0.04	0.74	29.14°	99.88±0.95
MF4	0.434±0.04	0.584±0.04	25.69±0.04	0.74	29.24°	99.27±0.27
MF5	0.424±0.03	0.574±0.03	26.13±0.03	0.73	29.34°	99.87±0.78
MF6	0.431±0.03	0.581±0.03	25.82±0.03	0.76	30.51°	99.57±0.98
MF7	0.436±0.02	0.576±0.02	24.31±0.02	0.75	29.17°	99.13±0.56

MF8	0.427±0.04	0.577±0.04	25.99±0.04	0.74	29.11°	98.26±0.89
MF8	0.427±0.04	0.577±0.04	25.99±0.04	0.74	29.11°	99.26±0.79
MF9	0.427±0.04	0.577±0.04	25.99±0.04	0.74	29.11°	99.26±0.59

Table 3 B: Characterisation of Granules of formulations of Glimepiride IR layer:

Formulation Code	Bulk Density	Tapped Density	Hausner's ratio	Carr's Index	Angle of repose (θ)	Drug Content
GF1	0.434±0.04	0.584±0.04	25.69±0.04	0.74	29.24°	99.27±0.09
GF2	0.424±0.03	0.574±0.03	26.13±0.03	0.73	29.34°	99.87±0.14
GF3	0.433±0.04	0.583±0.04	25.73±0.04	0.74	29.24°	99.23±0.14
GF4	0.432±0.04	0.582±0.04	25.77±0.04	0.74	29.14°	99.88±0.15
GF5	0.431±0.03	0.581±0.03	25.82±0.03	0.76	30.51°	99.57±0.12
GF6	0.436±0.02	0.576±0.02	24.31±0.02	0.75	29.17°	99.13±0.13
GF7	0.429±0.04	0.579±0.04	25.91±0.04	0.74	30.19°	98.89±0.15

2. Characterisation of Compressed Tablets

Table 4: Physical Characterization of bilayer Tablets.

Formulation Code (Primary)	Uniformity of weight	Length	Width	Thickness	Hardness	Friability
MF1	1389±0.92	21.5±0.04	9.75±0.06	7.8±0.2	12.8±0.2	0.12 %
MF2	1389±0.84	21.5±0.06	9.75±0.07	7.8±0.4	14.2±0.4	0.13 %
MF3	1389±1.04	21.5±0.07	9.75±0.08	7.8±0.6	14.8±0.6	0.14 %
MF4	1389±1.06	21.5±0.06	9.75±0.07	7.8±0.6	16.2±0.6	0.17 %
MF5	1389±1.12	21.5 ±0.05	9.75±0.08	7.8±0.8	16.2±0.8	0.16 %
MF6	1389±1.21	21.5±0.04	9.75±0.08	7.8±0.8	16.4±0.8	0.18 %
MF7	1389±0.86	21.5±0.03	9.75±0.07	7.8±0.6	16.2±0.6	0.19 %
MF8	1389±0.99	21.5±0.03	9.75±0.06	7.8±0.8	16.8±0.8	0.15 %
MF9	1389±0.99	21.5±0.03	9.75±0.06	7.8±0.2	16.6±0.8	0.15 %

Table 5 (A): Chemical Characterization of Tablets : Metformin hydrochloride.

Formulation Code	Drug Content (ASSAY)	Content Uniformity		
		Min.	Max.	Avg.
F1	99.27±0.74	98.57	101.02	99.55
F2	99.87±0.78	98.32	100.18	99.47
F3	99.57±0.84	98.25	100.13	99.32
F4	99.13±0.82	98.17	100.17	99.58
F5	98.89±0.91	98.16	100.24	99.23
F6	99.23±0.87	98.27	100.31	99.43
F7	99.88±0.78	98.32	100.58	99.31
F8	99.21±0.88	98.15	100.20	99.16
F9	99.52±0.88	98.15	100.20	99.16

Table 5 (B): Chemical Characterization of Tablets: Glimepiride IR Part.

Formulation Code	Drug Content (ASSAY)	Content Uniformity		
		Min.	Max.	Avg.
F1	99.27±0.74	98.57	101.02	99.55
F2	99.87±0.78	98.32	100.18	99.47
F3	99.57±0.84	98.25	100.13	99.32
F4	99.13±0.82	98.17	100.17	99.58
F5	98.89±0.91	98.16	100.24	99.23
F6	99.23±0.87	98.27	100.31	99.43
F7	98.26±0.88	98.15	100.20	99.16

Table 6 (A): Cumulative %drug released formulations of Metformin SR layer

Time In Hours	MF1	MF2	MF3	MF4	MF5	MF6	MF7	MF8	MF9
	%	%	%	%	%	%	%	%	%
1	53±0.22	46±0.25	41±0.36	39±0.11	36±0.22	29±0.74	27±0.51	25±0.24	35±0.31
2	84±0.34	79±0.36	72±0.22	65±0.21	62±0.24	57±0.21	53±0.22	43±0.21	57±0.31
4	96±0.21	90±0.34	87±0.23	81±0.34	79±0.17	71±0.31	69±0.32	64±0.31	88±0.31
8	--	--	--	96±0.51	92±0.24	89±0.35	87±0.27	81±0.43	92±0.31
12	--	--	--	--	--	--	--	98±0.41	

Table 6 (B): Cumulative %drug released formulations of Glimepiride IR layer.

Time In Min	GF1	GF2	GF3	GF4	GF5	GF6	GF7
	%	%	%	%	%	%	%
5	50±0.22	51±0.25	49±0.36	53±0.11	55±0.22	49±0.74	39±0.51
15	97±0.34	85±0.36	83±0.22	84±0.21	97±0.24	83±0.21	52±0.22

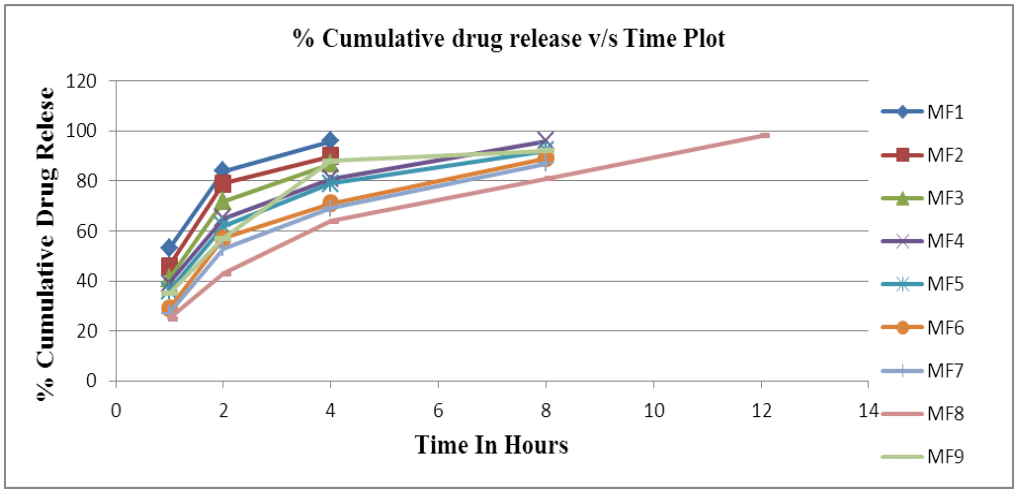

Figure 3: % Cumulative drug release v/s Time Plot for Metformin SR Layer.

Stability Studies

The optimized matrix tablets were subjected to stability studies(as per ICH guide lines) at 25°C ± 2°C / 60% ± 5% RH and 40°C ± 2°C / 75% ± 5% RH The products were evaluated for their.

DISCUSSION

In the present study an attempt has been to formulate and evaluate sustained release matrix tablets of Metformin HCl and Glimepride IR layer, employing hydrophilic polymers like Hydroxypropyl methylcellulose (HPMC K4M & HPMC K4M), along with pharmaceutically acceptable easily available inert excipients and nine formulations were prepared. The formulation was subjected to both pre and post formulation studies. The procured drug sample of Glimepiride and Metformin HCl was tested for its identification by means of organoleptic properties, melting point, UV spectra and FTIR spectrum.

CONCLUSION

A new sustained release tablet formulation (MF8) of Metformin hydrochloride has been developed and evaluated for its in vitro drug release. Extended release tablets were found to be an effective technique for a highly water-soluble drug Metformin hydrochloride. Bioavailability studies should be done to assess the usefulness of this formulation in comparison with existing market products of extended release Metformin hydrochloride. Immediate release of Glimepiride combined with Metformin hydrochloride SR layer the latter immediate formulation (GF5) also developed and successfully combined with primary SR part.

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