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ASSESSMENT OF BILAYER TABLETS OF GLIMEPIRIDE AND METFORMIN HYDROCHLORIDE WITH COMBINATION OF HYDROPHILIC AND HYDROPHOBIC POLYMERS BY HOT MELT EXTRUSION

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ABSTRACT

The purpose of the present study was to construct and assess bi-layered tablets of metformin hydrochloride as sustained release (SR) and glimepiride as immediate release form for the treatment of diabetic mellitus. Immediate release layer of glimepiride produced employing several super disintegrants. Prepared tablets were examined for normal pharmacopoeial evaluation tests. The employment of a hydrophobic carrier coupled with a hydrophilic polymer effectively regulates the initial rapid release of a highly water soluble medication like metformin HCl. SR granules were manufactured by hot melt extrusion method. Results demonstrated the complete and quick release of immediate release layer while sustaining effect for sustained layer observed for 10 hours. The drug release data subjected to several mathematical models to determine the kinetics of SR layer using a regression coefficient. The best matching model was Korsmeyer-Peppas suggesting non-fickian transport. Stability investigations and Fourier transform infrared examinations demonstrated absence of drug-polymer interaction. The current study successfully achieved the design and development of bilayer tablet formulation

Keywords: *Sustained Release, Immediate Release, Bilayered Tablets*

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1. INTRODUCTION

Bilayer pills are the medicines which consist of two similar or distinct substances mixed in a single dose for effective treatment of the ailment.

Type 2 diabetes mellitus is a diverse condition characterized by various abnormalities in the pancreatic β-cell, liver, and peripheral tissue such as skeletal muscles and adipose tissue. As combination therapy has many advantages over monotherapy such as problems of dose-dependent side effects are avoided. A low-dose combination of two distinct drugs decreases dose-related hazards; the addition of one agent may counterbalance some negative effects of the other. Using a modest dosage of two separate drugs decreases the clinical and metabolic effects that occur with maximal dosage of individual components of the combined tablet, and thus dosage of the single components can be lowered. The key therapeutic goals insubjects with Type 2 diabetes are to optimize blood glucose management, to minimize overweight, and to normalize lipid abnormalities and increased blood pressure. Multilayered tablet concept has long been applied to generate sustained release (SR) formulations. Such a tablet has quick releasing layer and may have the bi or triple layers, to sustain the medication release. The pharmacokinetic advantages rely on the requirement that drug release from the rapid releasing layer leads to a sudden rise in blood concentration. However, the blood level is kept at steady state, as the medication release from sustaining layer. Bi-layer tablet is suitable for sequential release of two medications in combination, separate two incompatible substances, and also for SR tablet in which one layer is immediate release as initial dosage and second layer is maintenance dose. The purpose of this research was to design a combination medication therapy for antidiabetic tablet formulation having various mechanism of actions to complement each other and jointly effectively lower the blood glucose levels. Metformin is an oral biguanide first-line choice of medicine. Metformin has an oral bioavailability of 50-60 percent under fasting conditions and is absorbed slowly. The average elimination half-life in plasma is 6.2 hours. Peak plasma concentrations (Cmax) are obtained within 4-8 hrs with extended-release formulations.

Glimepiride is one of the third-generation sulfonylurea medicines effective for treatment of diabetes mellitus, Type 2.

Preclinical studies of glimepiride showed a number of possible improvements over sulfonylurea currently available including lower dosage, quick onset probably due to reduced stimulation of insulin secretion and more apparent extra pancreatic effects. More recently, the method has been developed for the manufacture of pharmaceutical matrix systems offering instant or regulated drug release. Hot-melt extrusion (HME) has been adopted as a revolutionary approach for the formation of oral solid dosage forms in pharmaceutical companies in the previous decade. It was primarily employed in food and plastic industry but has received great interest in pharmaceutical manufacturing for the development of strong formulations. HME can be utilized to produce other formulations such as SR matrices. HME approach fits today's pharmaceutical business demand due to its simplicity, continuous and efficient process and due to various advantages over previous methods. The purpose of this work was to formulate and evaluate of bilayer tablet containing metformin HCl in SR form using hydrophobic polymer Eudragit RSPO and hydrophilic melting polymer PEG 6000 by HME process coupled with glimepiride rapid release layer.

2. MATERIALS AND METHODS

Materials

Metformin HCl and glimepiride were supplied from Wockhardt Research Center (Aurangabad, India) (Aurangabad, India). Kyron T-314, sodium starch glycolate, and croscarmellose sodium were received from Lincoln Pharmaceuticals Ltd, Ahmedabad, India. Eudragit RSPO was got as a nice gift sample from Evonik-Degussa (Mumbai) (Mumbai). Polyethylene (PEG) 6000, Magnesium stearate and citric acid were acquired from Golden Cross Pharma (Daman), India. Avicel PH-112 was purchased from Signet Chemicals, India. All additional chemicals/reagents used were of analytical grade, except for those employed in high-performance liquid chromatography (HPLC) analysis, which were of HPLC grade.

Experimental

Fourier Transform Infrared (FTIR) Spectroscopy

The infrared (IR) spectra were acquired using a FTIR spectrophotometer (Shimadzu IR affinity-1) in the wavelength band between 4000 and 400/cm. The spectra produced for drug, polymers, and a physical combination of drug with polymers was compared. IR spectra for medication, tablets were obtained in an FTIR spectrophotometer with KBr pellets.

Methods

Development of bilayer pill of metformin HCl and glimepiride was carried in two stages. Blends of SR layer of metformin HCl and rapid release layer of glimepiride were produced and compressed separately for preliminary evaluations\s. Preparation of the immediate release (IR) granules

For immediate layer, batches were prepared by dry blending of components followed by direct compression utilizing composition stated in Table 1. All the tableting excipients (minus lubricant) and medicament were combined geometrically by passing through 40# filter. Again, mixed in polybag for 5 minutes. Added the lubricants and stirred further for 2 minutes. Prepared blend left aside till compression.

Preparation of SR granules by hot melt extrusion

The anhydrous citric acid and medication were geometrically diluted with the polymers and combined in polybag. The mixes were manually fed through a hopper into an extruder and processed at temperaturesbetween 90 and 140°C, depending on the process capabilities of the formulation. The screw speed was set to a maximum of 20 rpm, while the motor load was limited to 0.700 drive amperes, and the pressure did not exceed 200 PSI. 16 mm co-rotating twin screw melt extruder was utilized for this purpose. The maximum processing temperature was chosen below the active pharmaceutical components melting range. The obtained granules were filtered

through appropriate screen. Diluted the granules with Avicel PH 112, blended and lastly lubricated. Formulation codes are presented in Table 2.

Preparation of bilayer tablet

Bi-layer tablets were compressed utilizing eight station tablet compression machine (India) coupled with 19 mm × 9 mm D tooling oblong shape die and punch. Immediate release layer was compressed first followed by SR layer.

Characterization of powder blend

The pre-compression characteristics of the powder blend were examined before compression of tablet. Precompression characteristics such as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio were determined for their micromeritic qualities

Table 1 Composition composition, in milligrams, for instant release layer for bilayer tablet

Ingredients	GF1	GF2	GF3
Glimepride	1	1	1
Sodium starch glycolate	4	-	-
Cross carmellose sodium	-	3	-
Kyron T-314	-	-	2
Avicel PH-112	92.5	93.5	94.5
Magnesium stearate	2	2	2
Red oxide of iron	0.5	0.5	0.5

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Table 2 The composition , in milligrams, for sustained release layer for bilayer tablet

Ingredients	MF1	MF2	MF3	MF4	MF5	MF6	MF7	MF8	MF9
Metformin HCl	500	500	500	500	500	500	500	500	500
Eudragit RSPO	80	96	112	80	96	112	80	96	112
PEG 6000	64	64	64	80	80	80	96	96	96
Citric acid	70	70	70	70	70	70	70	70	70
Avicel PH-112	82	66	50	66	50	34	50	34	18
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2

3. PARAMETERS OF EVOLUTION

In vitro evaluation of manufactured bilayer tablets

The weight variation of the pills was carried out using 20 tablets using an electronic balance. Friability was tested using 10 tablets in a Roche friabilator (Akums Drugs & Pharmaceuticals Limited) for 4 minutes at of 25 rpm. For each formulation, the hardness of 10 tablets was also tested using a hardness tester (Monsanto hardness tester) (Monsanto hardness tester). The thickness of the each 10 tablets was measured with a Vernier Caliper.

Drug content

Totally, 20 pills were weighed and finely powdered. The powder equivalent to 500 mg of metformin HCl and 1 mg of glimepiride were transferred to a separate 100 ml volumetric flasks. Added roughly 50 ml of diluents and sonicated to dissolve. Made up the volume up to the mark with diluent and mixed. Again diluted 1.0 ml of this solution to 100.0 ml with diluent and mixed.

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Acetonitrile was employed as diluent. The entire amount of medication within the pills was evaluated by modified HPLC technique.

4. RESULTS AND DISCUSSIONS

FTIR STUDY

The FTIR spectrum of glimepiride and metformin HCl in formulations was presented in Fig. 1. FTIR analyses found that metformin HCl showed two typical bands at 3369 and 3296/cm due to N-H primarystretching vibration and a band at 3170/cm due to N-H secondarystretching, and distinctive bands at 1626 and 1567/cm attributed to C=N stretching. No significant shifts of reduction in intensity of the FTIR bands of metformin hydrochloride were observed as indicated in Fig. 1 indicating of absence of drug polymer and drug-drug interactions.

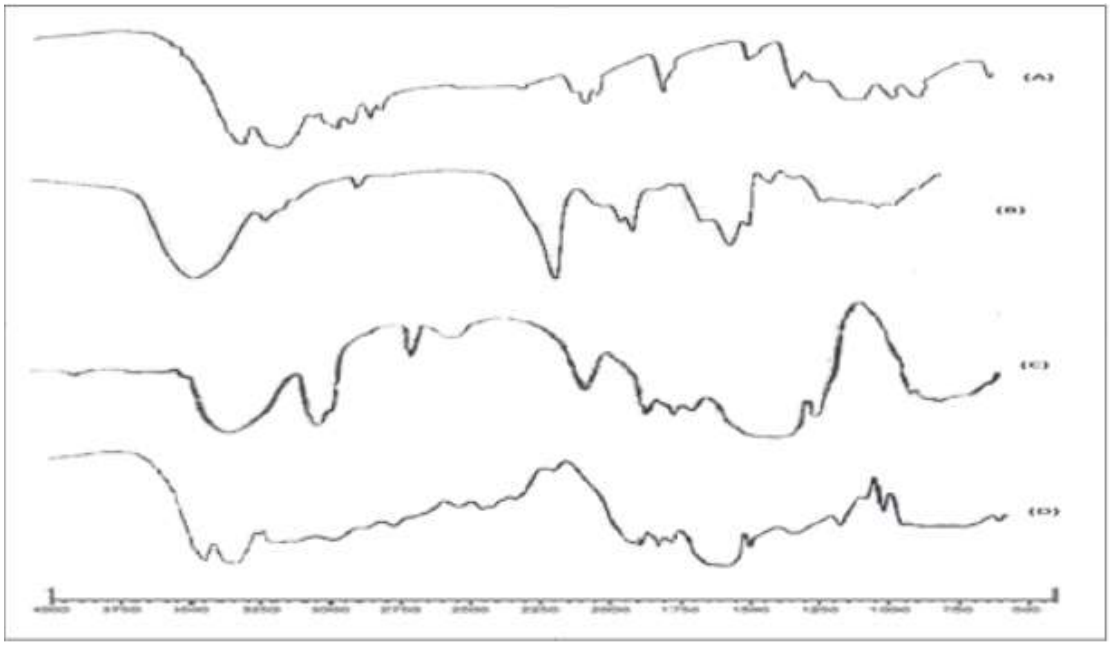

FIG 1 Fourier transform infrared spectrum of (a) Metformin (b) Glimepiride (c) Eudragit RSPO (d) Metformin+Glimepiride+Eudragit RSPO

Characterization of powder blend

Precompression characteristics (micromeritic properties) such as angle of repose, bulk density, tapped density; Carr's index and Hausner's ratio were determined. These are suggestive of compressibility and flow characteristics of pure medicines and manufactured granules. All the formulations demonstrated good compressibility and flow characteristics than pure drugs(Table 3).

Physicochemical properties of bilayer tablets The weight of IR layer was kept constant at 100 mg. The right choice of super disintegrants permitted speedy and full removal of IR layer from tablet. The thickness, friability and hardness of all tablets varied and observed to be 7.53±0.02 mm, 0.23±0.06 percent ,and 6.42 kg/cm2, respectively. The drug contents of tablets for glimepiride 98.45 percent and for metformin 96.31-100.02 percent which were well within the limits. The weight variation was observed to be0.34±0.02.

TABLE 3: Physicochemical properties of the prepared metformin and glimepiride granules

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (θ)	Carr's index (%)	Hausner's ratio
MF1	0.53	0.67	40.56	20.54	1.243
MF2	0.56	0.69	37.45	18.32	1.224
MF3	0.61	0.72	39.32	17.34	1.217
MF4	0.52	0.66	38.21	19.13	1.235
MF5	0.56	0.7	35.43	18.62	1.212
MF6	0.62	0.75	38.41	20.23	1.233
MF7	0.58	0.64	37.15	17.05	1.225
MF8	0.51	0.71	34.27	19.67	1.246
MF9	0.55	0.77	37.65	16.17	1.201
GF3	0.54	0.69	41.47	20.74	1.259

*All values are expressed as mean±standard deviation, n=3. MF6: Metformin formulations, GF: Glimepiride formulation

Release of drug studies

The release characteristics of glimepiride and metformin HCl from several batches of prepared matrix tablets were displayed in Figs. 2-4. For quick release layer, the order of improvement of

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the dissolution rate with several super disintegrants was determined to be Kyron T-314>crosscarmellose>sodium starch glycolate. The in vitrodisintegration time of the tablets IR layer was determined to <60 seconds. Based on these results, formulation glimepiride formulations (GF3) was selected for further testing. Citric acid monohydrate in SR layer was introduced as a solid-state plasticizer in HME Eudragit RSPO and PEG 6000 tablets.

Citric acid increased medication melting during extrusion through contact and melting point depression. All formulations demonstrated an initial modest burst impact with a considerably greater release, followed by an SR for the balance of the dissolving period independent of pH. The initial modest burst release can be connected with the release of drug from the surface of the tablet which exposed to the dissolution liquid, while diffusion processes prevailed at subsequent time periods. The metformin HCl layer with Eudragit RSPO at 14 percent , PEG 6000 at 10 percent gave about 90 percent of drug release after 10 hrs (Fig. 4). Based on these results, formulation GF3 was selected for future testing. The best batch from GF3 and metformin formulations was used to construct final bilayered tablet which approximated the dissolving properties of both the medicines when compressed alone.

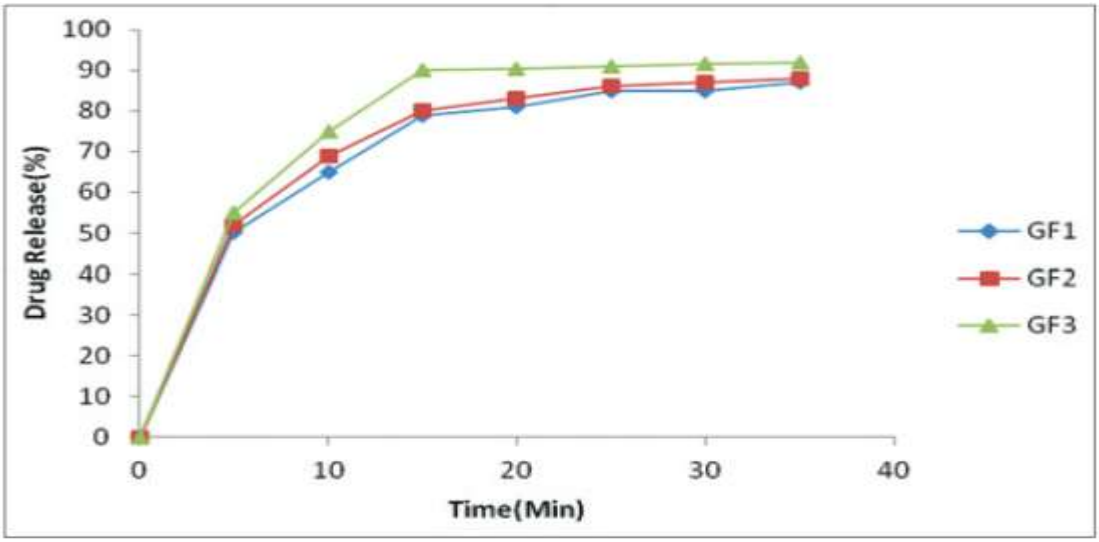

Fig 2 Impact of disintegrating agent on release profile of glimepiride from the bilayer matrix tablets

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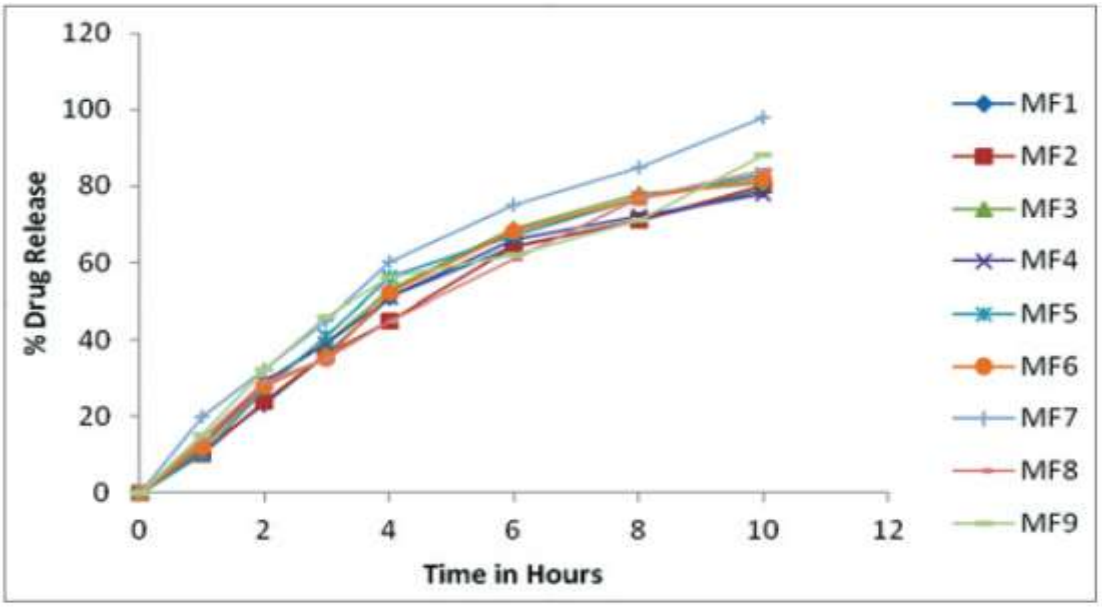

Fig 3 Impact of polymers concentrating on release profiles of metformin HCl sustained release layer from the bilayer matrix tablets

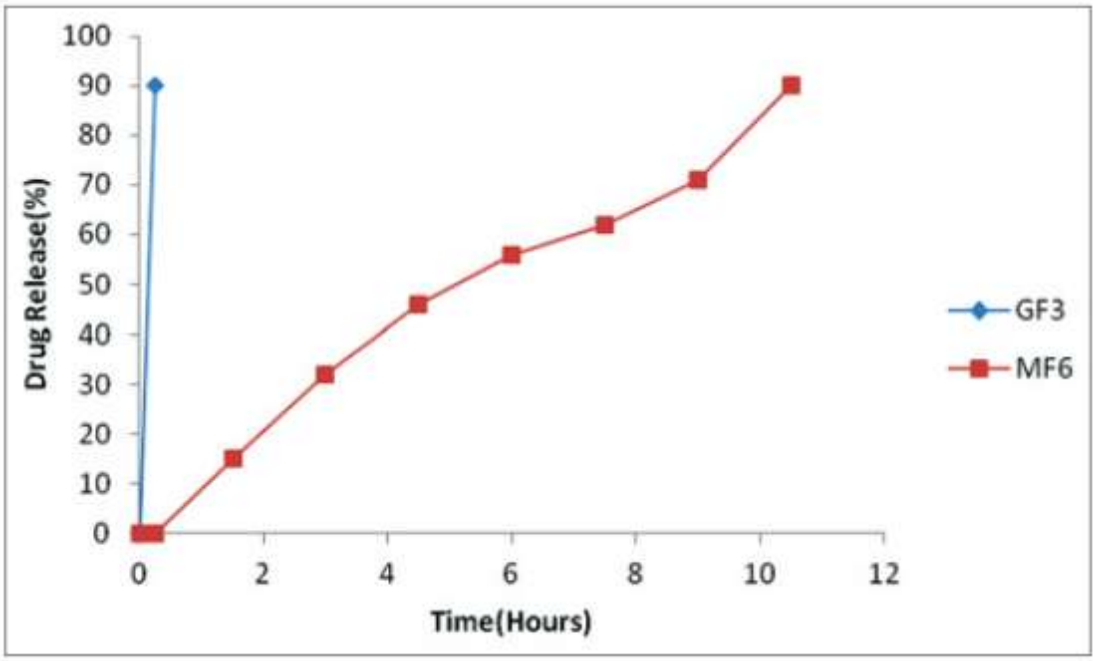

Fig 4 Impact on release of metformin HCI along with glimepiride from the bi-layer matrix tablets

5. CONCLUSION

Blayer tablet comprising metformin HCl SR layer and glimepiride was effectively created utilizing HME process using a combination of hydrophilic and hydrophobic polymers. The hydrophilic polymers regulated the release of metformin HCl for up to 10 hrs meant for once a day, glimepiride as immediate release and metformin HCl as SR suggested potential of both the medications in form of bilayer tablets; an alternative to the standard dose form. The superdisntegrant and hydrophilic polymers generated the appropriate release profile. The aforementioned technique has been demonstrated useful and capable to build unique delivery systems with the necessary release profiles for combination of medications treating the same ailment.

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