DESIGN AND EVALUATION 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 aim of the present study was to design and evaluate bilayered tablets of metformin hydrochloride as sustained release (SR) and glimepiride as immediate release form for the treatment of diabetes mellitus. Immediate release layer of glimepiride prepared using different super disintegrants. Prepared tablets were evaluated for routine pharmacopoeial evaluation tests. The use of a hydrophobic carrier along with a hydrophilic polymer effectively controls the initial rapid release of a highly water soluble drug like metformin HCl. SR granules were prepared by hot melt extrusion technique. Results confirmed the complete and rapid release of immediate release layer while sustaining effect for sustained layer observed for 10 hrs. The drug release data subjected to various mathematical models to determine the kinetics of SR layer using a regression coefficient. The best fit model was Korsmeyer-Peppas indicating non-fickian transport. Stability studies and Fourier transform infrared studies indicated absence of drug-polymer interaction. The current study successfully achieved the design and development of bilayer tablet formulation.

Keywords: Sustained release, Immediate release, Hot melt extrusion, Eudragit RSPO, PEG 6000, Bilayer.

INTRODUCTION

Type 2 diabetes mellitus is a heterogeneous disorder characterized by multiple defects in the pancreatic β-cell, liver, and peripheral tissue such as skeletal muscles and adipose tissue. As combination therapy has various advantages over monotherapy such as problems of dose-dependent side effects are minimized. A low-dose combination of two different agents reduces dose-related risks; the addition of one agent may counteract some deleterious effects of the other. Using a low dosage of two different agents minimizes 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 reduced [1,2]. The major therapeutic goals in subjects with Type 2 diabetes are to optimize blood glucose control, to reduce overweight, and to normalize lipid disturbances and elevated blood pressure [3]. Multilayered tablet concept has long been utilized to develop sustained release (SR) formulations. Such a tablet has fast releasing layer and may contain the bi or triple layers, to sustain the drug release. The pharmacokinetic advantages rely on the criterion that drug release from the fast releasing layer leads to a sudden rise in blood concentration. However, the blood level is maintained at steady state, as the drug release from sustaining layer. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances, and also for SR tablet in which one layer is immediate release as initial dose and second layer is maintenance dose [4-6]. The objective of this research was to develop a combination drug therapy for antidiabetic tablet formulation having different mechanism of actions to complement each other and together effectively lower the blood glucose levels. Metformin is an oral biguanide first-line choice of drug. Metformin has an oral bioavailability of 50-60% under fasting conditions and is absorbed slowly [7,8]. The average elimination half-life in plasma is 6.2 hrs. Peak plasma concentrations (C_{max}) are reached within 4-8 hrs with extended-release formulations. Glimepiride is one of the third-generation sulfonylurea drugs useful for control of diabetes mellitus, Type 2. Preclinical investigation of glimepiride suggested a number of potential benefits over sulfonylurea currently available including lower dosage, rapid onset possibly due to less stimulation of insulin secretion and more pronounced extra pancreatic effects [9]. More recently, the process has been adapted for the preparation of pharmaceutical matrix systems providing immediate or controlled drug release. Hot-melt extrusion (HME) has been employed as a novel technique for the formulation of oral solid dosage forms in pharmaceutical industries in the last decade. It was initially used in food and plastic industry but has attracted significant interest in pharmaceutical manufacturing for the development of robust formulations. HME can be used to develop various formulations such as SR matrices [10-13]. HME method fulfills today's pharmaceutical industry need due to its simplicity, continuous and efficient process and due to many advantages over conventional methods [14,15]. The objective of present study was to formulate and evaluation of bilayer tablet containing metformin HCl in SR form using hydrophobic polymer Eudragit RSPO and hydrophilic melting polymer PEG 6000 by HME method along with glimepiride immediate release layer.

METHODS

Materials

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

Experimental

Fourier transform infrared (FTIR) spectroscopy

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

Methods

Development of bilayer tablet of metformin HCl and glimepiride was carried in two stages. Blends of SR layer of metformin HCl and immediate release layer of glimepiride were prepared and compressed separately for preliminary evaluations.

Preparation of the immediate release (IR) granules

For immediate layer, batches were prepared by dry blending of ingredients followed by direct compression using composition outlined in Table 1. All the tableting excipients (without lubricant) and drug were mixed geometrically by passing through 40# sieve. Again, mixed in polybag for 5 minutes. Added the lubricants and mixed further for 2 minutes. Prepared blend kept aside till compression.

Preparation of SR granules by hot melt extrusion

The anhydrous citric acid and drug were geometrically diluted with the polymers and blended in polybag. The blends were manually fed through a hopper into an extruder and processed at temperatures between 90 and 140°C, depending on the process ability 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 used for this purpose [16]. The maximum processing temperature was set below the active pharmaceutical ingredients melting range. The obtained granules were screened through suitable screen. Diluted the granules with Avicel PH 112, mixed and finally lubricated. Formulation codes are provided in Table 2.

Preparation of bilayer tablet

Bi-layer tablets were compressed using eight station tablet compression machine (Cadmach, India) fitted 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 parameters of the powder blend were evaluated before compression of tablet. Precompression parameters such as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio were determined for their micromeritic properties.

Evaluation parameters

In vitro evaluation of prepared bilayer tablets

The weight variation of the tablets was carried out with 20 tablets using an electronic balance (Shimadzu, Japan). Friability was determined using 10 tablets in a Roche friabilator (Pharma Lab, Ahmadabad, India) for 4 minutes at of 25 rpm. For each formulation, the hardness of 10 tablets was also evaluated using a hardness tester (Monsanto hardness tester). The thickness of the each 10 tablets was measured with a Vernier Caliper [17,18].

Drug content

Totally, 20 tablets 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 about 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. Acetonitrile was used as diluent. The total amount of drug within the tablets was analyzed by modified HPLC method [19].

In vitro dissolution studies

Chromatographic conditions

Apparatus: HPLC.

Column: 150 mm × 4.6 mm, 5 µm, C18, ODS.

Flow rate: 1.0 ml/minutes.

Temperature: 250 C.

Injected volume: 10 µL.

Detector: 225 nm.

Retention time: About 4.5 minutes metformin and 8.6 minutes glimepiride.

Buffer preparation: Buffer was prepared by dissolving 3.9 g of sodium dihydrogen phosphate in 1 L of water adjusted to pH 6.0 using diluted sodium hydroxide solutions.

Diluent: Acetonitrile was used as diluents.

Mobile phase: Filtered and degassed mixture of buffer and acetonitrile (600:400).

Release of glimepiride was determined using a dissolution apparatus type II at 100 rpm. The dissolution was studied using 900 ml of 0.1 N hydrochloric acid. The temperature was maintained at 37±0.5°C. A sample (5 ml) was withdrawn at different time intervals, i.e., 5, 15, 30, 45 minutes, filtered through Whatman filter paper and replaced by an equal volume of dissolution medium. Samples were suitably diluted and analyzed for glimepiride content using chromatogram. The percentage of glimepiride release was calculated.

Release of metformin hydrochloride was determined using a dissolution apparatus type II at 100 rpm. The dissolution was studied using 900 ml of phosphate buffer pH 6.8. The temperature was maintained at 37±0.5°C. The sample (5 ml) was withdrawn at different time intervals, i.e., 1, 2, 3, 4, 5, 6, 7, and 8 hrs, filtered through Whatman filter paper

Table 1: The composition, in milligrams, for immediate 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

GF: Glimepiride formulation

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

MF: Metformin formulation

and replaced by an equal volume of dissolution medium. Samples were suitably diluted and analyzed for metformin hydrochloride content using chromatogram [20].

Dissolution data analysis

Metformin dissolution kinetics was analyzed by various mathematical models. In model-dependent approaches, release data were fitted to five kinetic models including zero-order, first-order, Higuchi's equation, Korsmeyers-Peppas, and Hixson-Crowell release equation to find the higher correlation ($r^2 > 0.98$), release exponent (n), and rate constant (k_1) for all formulations which were applied considering the amounts of drug released from 0 to 10 hrs. The model with the highest correlation coefficient was considered to be the best fitting one.

Zero-order equation:

$$Q_t = Q_0 + k_0 t \ldots (1)$$

Where, Q_t is the amount of drug release in time t, Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and k_0 is the zero-order release rate.

First-order equation:

$$\ln Q_t = \ln Q_0 = k_1 t \ldots (2)$$

Where, Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the solution and k_1 is the first order release rate constant.

Higuchi's equation:

$$Q = k_H t^{1/2} \ldots (3)$$

Where, Q is the amount of drug release at time t, and k_H is the Higuchi diffusion rate constant [20].

Koresmeyer's equation:

$$M_t/M_\infty = Kt^n \ldots (4)$$

Where, M_t is the amount of drug released at time t, M_∞ is the amount of drug released after infinite time, k is a kinetic constant incorporating structural and geometric characteristics of the tablet, and n is the diffusional exponent indicative of the drug release mechanism [21].

Accelerated stability studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions [22,23]. An accelerated stability study was conducted by wrapping the tablets in aluminum foils and kept at 25°C/60% RH and 40°C/75% RH. Tablets were checked for appearance, thickness, and hardness. In addition, drug content and the dissolution tests were performed periodically for 3 months and compared with initials.

RESULTS AND DISCUSSION

FTIR study

The FTIR spectrum of glimepiride and metformin HCl in formulations was shown in Fig. 1. FTIR studies revealed that metformin HCl showed two typical bands at 3369 and 3296/cm due to N-H primary stretching vibration and a band at 3170/cm due to N-H secondary stretching, and characteristics bands at 1626 and 1567/cm assigned to C=N stretching. No significant shifts of reduction in intensity of the FTIR bands of metformin hydrochloride were observed as shown in Fig. 1 indicative of absence of drug polymer and drug-drug interactions.

Characterization of powder blend

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

Physicochemical properties of bilayer tablets

The weight of IR layer was kept constant to 100 mg. The proper choice of super disintegrants allowed rapid and complete release 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%, and 6.42 kg/cm², respectively. The drug contents of tablets for glimepiride 98.45% and for metformin 96.31-100.02% which were well within the limits. The weight variation was observed to be 0.34±0.02.
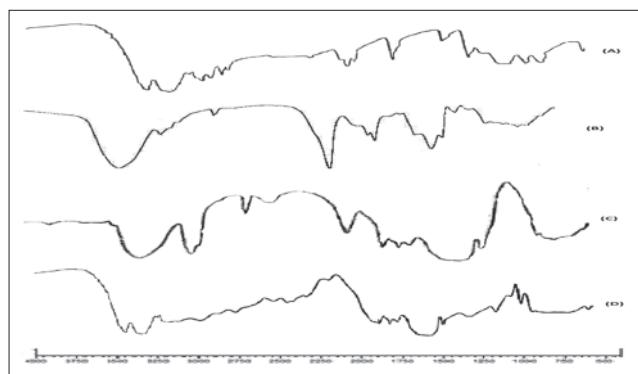

Fig. 1: Fourier transform infrared spectrum of (a) Metformin (b) Glimepiride (c) Eudragit RSPO (d) Metformin+Glimepiride+Eudragit RSPO

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

Drug release studies

The release profiles of glimepiride and metformin HCl from different batches of formulated matrix tablets were plotted in Figs. 2-4. For immediate release layer, the order of enhancement of the dissolution rate with various super disintegrants was found to be Kyron T-314>crosscarmellose>sodium starch glycolate. The *in vitro* disintegration time of the tablets IR layer was found to <60 seconds. Based on these results, formulation glimepiride formulations (GF3) was selected for further studies.

Citric acid monohydrate in SR layer was added as a solid-state plasticizer in HME Eudragit RSPO and PEG 6000 tablets. Citric acid promoted drug melting during extrusion by interaction and melting point depression [23].

All formulations showed an initial slight burst effect with a relatively higher release, followed by an SR over the remainder of the dissolution period independent of pH. The initial slight burst release can be correlated with the release of drug from the surface of the tablet which exposed to the dissolution medium, while diffusion processes dominated at later time points. The metformin HCl layer containing Eudragit RSPO at 14%, PEG 6000 at 10% gave about 90% of drug release after 10 hrs (Fig. 4). Based on these results, formulation GF3 was selected for further studies. The best batch from GF3 and metformin formulations was used to prepare final bilayered tablet which mimicked the dissolution profiles of both the drugs when compressed alone.

Drug release kinetics

After studying the different models, the zero order "R" values was 0.971, first order release in "R" value 0.989, the Higuchi's diffusion equation "R" value of 0.968. To con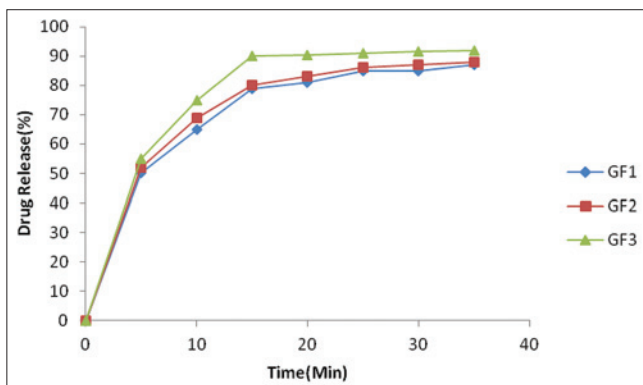firm the diffusion mechanism, the data were fitted into Korsmeyer's model. Korsemeyer-Peppas plot was 0.9921. The *in vitro* release profiles of drug could be best expressed by highest regression coefficient values for Korsemeyer-Peppas model hence it indicates that swelling diffusion is the predominant mechanism of drug release. For matrix tablets, an n value of near 0.5 indicates diffusion control, and an n value of near 1.0 indicates erosion or relaxation control.

Stability studies

Stability studies showed that there was no significant change in physical characteristics, percent drug release. Based on these results, it was concluded there were no appreciable change in drug content and *in vitro* release during the study period (30, 60, and 90 days) (Fig. 5).

CONCLUSION

Bilayer tablet of metformin HCl SR layer and glimepiride was successfully developed using HME method with a combination of hydrophilic and hydrophobic polymers. The hydrophilic polymers controlled the release of metformin HCl for up to 10 hrs intended for once a day, glimepiride as immediate release and metformin HCl as SR indicated potential of both the drugs in form of bilayer tablets; an alternative to the conventional dosage form. The superdisntegrant and hydrophilic polymers gave the desired release profile. The aforementioned technique has been proved advantageous and capable to develop novel delivery systems with the desired release profiles for combination of drugs treating the same disease.

Fig. 2: Effect of disintegrating agent on release profile of glimepiride from the bilayer matrix tablets

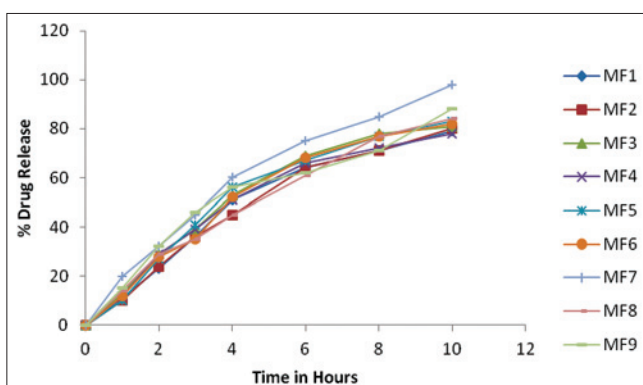**Fig. 3: Effect of polymers concentration on release profiles of metformin HCl sustained release layer from the bilayer matrix tablets**
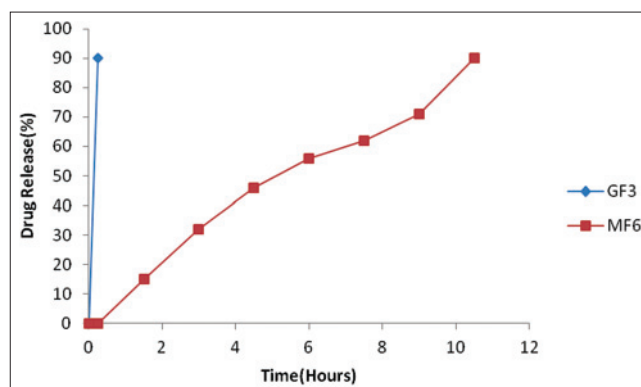

Fig. 4: Effect of polymers on release profile of metformin HCl along with glimepiride from the bilayer matrix tablets

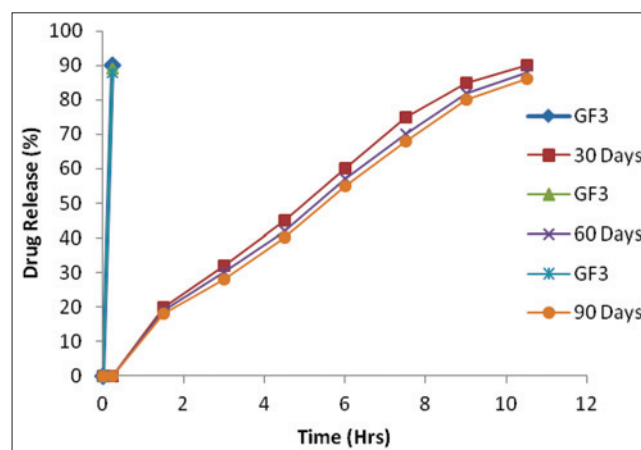**Fig. 5: The *in vitro* release study was observed even after the evaluation for 30, 60, and 90 days for stability**

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