Research Paper

Formulation and Release Characteristic of a Bilayer Matrix Tablet Containing Glimepride Immediate Release Component and Metformin Hydrochloride as Sustained Release Component

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ABSTRACT: The aim of present study was to design the concept of bilayered tablets containing Glimepride for immediate release using sodium starch glycolate as super disintegrant and Metformin hydrochloride (HCl) for sustained release by using Hydroxyl propyl methyl cellulose (HPMC K 4M) and Sodium Carboxy Methyl cellulose (SCMC) as the matrix forming polymer, and PVPK-30 as binder. The tablets were evaluated for physicochemical properties. All the values were found to be satisfactory. In vitro release studies were carried out as per USP in pH 1.2 with (0.1% sodium lauryl sulphate w/v) and phosphate buffer pH 6.8 using the apparatus I. The release kinetics of Metformin HCl was evaluated using the regression coefficient analysis. The formulated tablets (F5) shows zero order release and diffusion was the dominant mechanism of drug release. The polymer (HPMC K4M, SCMC) and binder PVPK-30 had significant effect on the release of Metformin HCl matrix tablets (F5). Thus formulated bilayer tablets provided immediate release of Glimepride and Metformin HCl as sustained release over a period of 8 hours. Stability studies and FT-IR studies clearly indicated that there is no drug – polymer interaction.

KEYWORDS: Bilayered tablets; Metformin HCl; Glimepride; Sustained released matrix tablets; Higuchi equation

Introduction

Type 2 diabetes is a progressive illness and most patients will eventually need more than two oral agents to maintain adequate glucose control (Tripathi K.D, 2004). Switching from one drug to another in a patient with poorly controlled glycemia or maximizing the dosage of an existing drug is only rarely hopeful. Adding medications from different groups to the existing regimen often provides more effective glycemic control. Several of the available oral agents have been studied in combination and have been shown to further improve glycemic control when compared with monotherapy.

Glimepride is one of the third generation sulfonylurea drug (Massimo et al., 2003; Kouichi et al., 2005) useful for control of diabetes mellitus, type 2. Preclinical investigation of glimepride suggested a number of potential benefits over sulfonylureas currently available including lower dosage, rapid onset possibly due to less stimulation of insulin secretion and more pronounced extra pancreatic effects.

Metformin hydrochloride is an orally administered biguanide, which is widely used in the management of type 2 diabetes (Stith et al., 1996). It is a hydrophilic drug and is slowly and incompletely absorbed from the gastrointestinal tract, and the absolute bioavailability of a single 500 mg dose is reported to be 50% to 60% (Dunn et al., 1995). The compound also has relatively short plasma elimination half-life of 1.5 to 4.5 hours (Defang et al., 2005; Scheen et al., 1996), hence Metformin HCl has to be administered two or three times per day. A sustained release (SR) formulation that would maintain plasma levels of the drug for 10 to 16 hours might be sufficient for once-daily dosing of Metformin. In particular, SR formulation that releases Metformin HCl for 8 to 12 hours may be suitable for once-daily dosing. SR products are needed for Metformin HCl to delay its duration of action and to improve patient compliance (Montvale, 1999; Dunn et al., 1995). A Glimepride and Metformin HCl combination is used to treat high blood sugar levels that are caused by type 2 diabetes. Normally, the pancreas release insulin after eating to help the body store excess sugar for later use.

This process occurs during normal digestion of food. In type 2 diabetes, the body does not work properly to store the excess sugar and the sugar remains in the bloodstream. Chronic high blood sugar can lead to serious health problems in the future. With two different modes of action, the combination of Glimepride and Metformin HCl help the body cope with high blood sugar more efficiently (Charpentier et al., 2001). Immediate action of Glimepride
will be helpful to control excess sugar, which will be maintained by Metformin HCl action later on. Thus, the developed single tablet will be sufficient instead of two to three tablets of both drugs per day, and it will also increase patient compliance and therapeutic efficacy.

The aim of the current research work is to study the release characteristics of a bilayer matrix tablet containing Glimepride as IR component and Metformin HCl as SR component in the form of matrix tablet, using a mixture of hydrophilic polymers (HPMC K4M and SCMC), by wet granulation method.

Materials and Methods

Materials

Metformin HCl and Glimepride were received from Mederich Sterilab Pvt Lab, Bangalore, Hydroxy Propyl Methyl Cellulose (HPMC K 4M) and Sodium Carboxy methyl cellulose (SCMC) was a gift sample received from Shinetsu Japan., and M/S Colorcon Asia Pvt. Ltd., Mumbai, India. respectively. Starch, polyvinyl pyrrolidone K-30 (PVP K-30), Dicalcium phosphate, aerosil, starch, sodium starch glycolate, MCCP, Pharmatose DCL 15, and Indico carmellose lake were purchased from S. D. Fine Chemicals Ltd., Mumbai, India. Magnesium stearate and talc were procured from Whitekal and Company, Hyderabad, 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.

Calculation of the Theoretical Release Profile of Metformin From Bilayer Tablets

The total dose of Metformin for a once-daily SR formulation was calculated by the following equation (Rawlins, 1997) using available pharmacokinetic data (Defang et al., 2005).

\[ D_t = \text{Dose} \times \left(1 + \frac{(0.693 \times t)}{t_{1/2}}\right) \]

Where, \(D_t\) = total dose of drug; \(\text{Dose}\) = dose of the IR part; \(t\) = time (hr) during which the SR is desired (8 hr); and \(t_{1/2}\) = half-life of the drug (3 hr).

\[ D_t = 175.6 \times \left(1 + \frac{[0.693 \times 8]}{3}\right) \approx 500. \]

Hence, the formulation should release 175.6 mg in 1 hour like conventional tablets and 46.3 mg per hour up to 8 hours thereafter.

Methodology

Preparation of Bilayered Tablets

Blends of the IR layer

Composition of the IR layer is given in Table 1. The final weight of the IR layer was fixed to 300 mg. Glimepride, sodium starch glycolate, and indico carmellose were passed through a mesh (1150µm) and blended in a planetary mixer for 5 minutes, so that the distribution of indico carmellose throughout the mass was uniform. The blend was sized by a mesh (250 µm) and mixed with, Pharmatose (DCL-15), talc and magnesium stearate for 2 minutes.

Granulation of the SR Layer.

Compositions of different trial formulations for the SR layer are given in Table 2. Different ratios HPMC and SCMC polymers were sifted with Metformin HCl, di calcium phosphate (DCP), and PVP K-30 through a mesh (1150 µm), and blended in a planetary mixer for 5 minutes. The sifted blend was granulated with isopropyl alcohol: methylene chloride (1:1), and the resulting wet coherent mass was sieved using a mesh (100 µm) and dried at 40°C for about 2 hours with a residual moisture content of 2% to 3% w/w. The dried granules were sized by a mesh (250 µm) and lubricated with magnesium stearate, aerosil and talc for 2 minutes. The final lubricated blend was subjected to compression with suitable tablet tooling with fill weight of 850 mg.

Table 1 Composition of various trials formulations for the IR layer containing 1mg glimepride

(All Quantities given in mg).

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulation code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N1</td>
</tr>
<tr>
<td>Glimepride</td>
<td>1</td>
</tr>
<tr>
<td>Sodium Starch glycolate</td>
<td>7.50</td>
</tr>
<tr>
<td>MCCP</td>
<td>61.0</td>
</tr>
<tr>
<td>Pharmatose DCL-15</td>
<td>228</td>
</tr>
<tr>
<td>Mg Stearate</td>
<td>1.25</td>
</tr>
<tr>
<td>Indico Carmellose (blue lake)</td>
<td>1.25</td>
</tr>
<tr>
<td>Total weight</td>
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</tbody>
</table>
Table 2 Composition of various trials formulations for the SR layer containing 500mg Metformin HCl
(All Quantities given in mg).

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulation code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
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<tr>
<td>Metformin Hcl</td>
<td>500</td>
</tr>
<tr>
<td>HPMC K4M</td>
<td>60</td>
</tr>
<tr>
<td>SCMC</td>
<td>120</td>
</tr>
<tr>
<td>Starch</td>
<td>100</td>
</tr>
<tr>
<td>PVP K-30</td>
<td>08</td>
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<tr>
<td>DCP</td>
<td>52</td>
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<tr>
<td>Aerosil</td>
<td>1</td>
</tr>
<tr>
<td>Mg Stearate</td>
<td>4</td>
</tr>
<tr>
<td>Talc</td>
<td>5</td>
</tr>
<tr>
<td>Total weight</td>
<td>850</td>
</tr>
</tbody>
</table>

Compression of Bilayer Tablets

Granules of both layers thus obtained were compressed into bilayered tablets using 19.5×8.9 mm size caplet punches and corresponding dies on double rotary tablets punching machine. Formulation code for the final bilayer tablet was named F1 to F5, where composition of F1 is SR1 for the SR layer and IR1 for the IR layer (F0 = SR0+IR0, where n = 1 to 5).

Physico chemical properties of prepared 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, Ahmedabad, India) for 4 minutes at a speed of 25 rpm. For each formulation, the hardness of 10 tablets was also evaluated using a hardness tester (Pfizer). The thickness of the each 10 tablets was measured with a Vernier Caliper.

Drug Content (REF)

Twenty tablets were taken and crushed to powder with a mortar and pestle. The exact amount of powder (around 1150 mg) was taken and diluted with 0.1 N sodium hydroxide (NaOH) up to 100 ml of volumetric flask. After sonication for 15 minutes, the solution was filtered through 0.45-µm filter paper. The total amount of drug within the tablets was analyzed after appropriate dilution of the test solution by using the modified HPLC method (Bhaskar Laxman rao et al., 2005).

In vitro dissolution studies

An in vitro drug release study from the prepared bilayered tablets was determined using the USP I (basket) apparatus (Lab India, DISSO2000). With 900 ml of pH of 1.2 with 0.1% w/v sodium lauryl sulphate and, followed by phosphate buffer pH 6.8 was used as dissolution media and maintained at 37±0.5°C at a rotational speed of 100 rpm, for 45mins and 8hrs respectively. Dissolution Samples were analyzed by HPLC method.

HPLC Method

Chromatographic conditions:
- Column: C8 column (Phenominex) (250 × 4.6 mm, 5µm particle size)
- Mobile phase: 10 m mol phosphate buffer of pH 2.5: Acetonitrile (50: 50 (v/v))
- Detector: UV detection at 228 nm
- Loop size: 20 µl

Stock solutions of Glimepride and Metformin HCl were prepared in 0.1 N NaOH as 1mg/ml. calibration curve was prepared for each of the analytes after appropriate dilution of stock solutions to obtain final concentrations of 0.1, 0.2, 0.5, 1, 2, 5, and 10 µg/ml for Glimepride and 0.1, 0.5, 1, 2, 5, 10, and 20 µg/ml for Metformin HCl. The calibration curve was prepared taking the peak area of the analytes (Glimepride/ Metformin HCl) versus the concentration (µg/ml) using a weighted (1/concentration^2) linear least-squares regression as the mathematical model. The regression equation of the calibration curve was then used to calculate the drug content and in vitro drug release. The lowest limit of quantitation for Glimepride and Metformin HCl was determined from the peak signal to noise level (S/N) as 10.

FT-IR Study

Infrared spectrum was taken (FT-IR, Spectrum RX1, Perkin Elmer Ltd, Switzerland) by scanning the sample in Potassium bromide discs. The samples of pure drug and formulated tablets were scanned individually.

Stability Study

An accelerated stability study was conducted by storing tablets in amber bottles at 25°C/60% RH and 40°C/75% RH. The content of the drugs and the dissolution of the drugs from the bilayer tablets were tested monthly for three months.
Drug Release Kinetics

To study the mechanism of Metformin release from the SR layer of the matrix tablets, the release data were fitted to the following equations:

Zero-order equation:

\[ Q_t = Q_0 + k_0 t \]  \hspace{1cm} \text{……(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:

\[ \ln Q_t = \ln Q_0 = k_1 t \]  \hspace{1cm} \text{……(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:

\[ Q = k_H t^{1/2} \]  \hspace{1cm} \text{……(3)}

Where, \( Q \) is the amount of drug release at time \( t \), and \( k_H \) is the Higuchi diffusion rate constant (12).

Koresmeyer’s equation:

\[ M_t / M_\infty = K_t^n \]  \hspace{1cm} \text{……(4)}

Where, \( M_t \) is the amount of drug released at time \( t \), \( M_\infty \) 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 (Korsmeyer et al., 1977).

Results and Discussion

The FT-IR spectrum of Glimepride and Metformin HCl in formulations (N3 & F5) was shown in figure 7 and 8. The spectra revealed the presence of peaks at 3369 cm\(^{-1}\) and 1495 cm\(^{-1}\) respectively, indicating that there was no interaction between the drug-excipients used in the study.

Table Characteristics

An IR layer of less than 250 mg caused incomplete Glimepride release due to sticking of the IR layer with the polymer of the SR layer, thus optimum weight of the IR layer was fixed to 300 mg for better release of Glimepride. Indico carmellose was used to differentiate two layers separately. DCP was used as filler and PVPK-30 was used as a binder. The tablets of different formulations were subjected to various evaluation tests such as thickness, hardness, friability, and drug content. The results of these parameters are given in Table 3. All the formulations showed uniform thickness. The average percentage deviation of all tablet formulations was found to be within the limit. Hence all the formulations passed the uniformity of weight. Tablet hardness is not an absolute indicator of strength (Banker, 1987). Another measure of a tablet’s strength is friability. Friability of the tablets was evaluated by using Roche friabilator, the percentage of friability for all the formulations was below 1%, indicating that the friability was within the prescribed limits (USP 2000).

In vitro Drug Release Study

Dissolution samples were analyzed by HPLC method. For Glimepride, the concentration range was 0.1 to 10 mcg/ml and the correlation coefficient was 0.99 (\( y = 80.271x + 1.99 \)). For Metformin HCl, the standard curves were linear over the concentration ranges of 0.1 to 20 mcg/ml and the correlation coefficient was 0.99 (\( y = 856.5x + 23.79 \)). The lower limit of quantitation for Glimepride was 40ng/ml, and its precision (CV %) and accuracy (%RE) values being 5.27% and +2.40% respectively. The lower limit of quantitation for Metformin HCl was 50ng/ml, its precision (CV %) and accuracy (%RE) values being 6.59% and +3.83%, respectively.

The representative chromatogram of a dissolution sample showing separation of Glimepride at 5.11 minutes and Metformin HCl at 2.26 minutes was shown in figure 1 and 2. There is no interfering peak in the chromatogram and the resolution between the two analyte peaks is good. Figure 3 shows Glimepride release from the immediate release (IR) formulations (N1 to N3). The percentage in vitro drug release from formulations N1 to N3 ranged from 96.3±1.12% and 99.07±1.15%. Complete Glimepride release occurred within 45 minutes, from the N3 formulation. It may attributed to the higher concentration of sodium starch glycrolate which supported the concept of IR from the bilayer tablets. Hence N3 formulation is opted for IR layer.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Weight variation Mean ±SD</th>
<th>Thickness (mm)</th>
<th>Hardness Kg/cm(^2)</th>
<th>Friability (%)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Glimepride</td>
</tr>
<tr>
<td>F1</td>
<td>0.48±0.03</td>
<td>8.45±0.02</td>
<td>9.02±0.17</td>
<td>0.27±0.05</td>
<td>98.32±0.15</td>
</tr>
<tr>
<td>F2</td>
<td>0.68±0.03</td>
<td>8.48±0.05</td>
<td>8.49±0.18</td>
<td>0.17±0.04</td>
<td>99.41±0.03</td>
</tr>
<tr>
<td>F3</td>
<td>0.33±0.02</td>
<td>8.52±0.01</td>
<td>9.00±0.23</td>
<td>0.21±0.06</td>
<td>98.75±0.09</td>
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<tr>
<td>F4</td>
<td>0.21±0.04</td>
<td>8.56±0.04</td>
<td>8.56±0.32</td>
<td>0.19±0.03</td>
<td>97.98±0.17</td>
</tr>
<tr>
<td>F5</td>
<td>0.44±0.02</td>
<td>8.54±0.06</td>
<td>9.01±0.12</td>
<td>0.23±0.04</td>
<td>99.01±0.12</td>
</tr>
</tbody>
</table>
**Fig. 1** Representative chromatogram showing separation of Glimepride at 5.11 minutes.

**Fig. 2** Representative chromatogram showing separation of Metformin HCl at 2.26 minutes.

**Fig. 3** Effect of disintegrating agent on release profile of Glimepride from the bilayer matrix tablets (bars represent ±SD (n=3))
Complete release of Metformin occurred from the bilayer tablets within 8 hours. The amount of HPMC K4M, SCMC polymers and PVPK-30 as binder in the formulation (F5) was found to affect the Metformin release rate. Tablets prepared with HPMC K4M (60 mg/tablet) in the SR layer released the drug slowly in dissolution medium, leading to sustained drug release. From figure 4 it is evident that as the anionic SCMC in the formulations increased, the percent of Metformin HCl release was found to decrease resulting in a greater controlled release. For obtaining a desirable drug release profile, a mixture of hydrophilic polymers in the ratio of 7.05:26.4%, (HPMC K4M: SCMC) was selected as the release controlling polymers.

![Graph showing cumulative drug release over time](image)

**Fig. 4** Effect of polymer mixture on release profile of Metformin HCl from the bilayer matrix tablets (bars represent ±SD (n=3))

**Release Profile of Metformin from Bilayer Tablets**

The theoretical release profile calculation is important to evaluate the formulation with respect to release rate and to ascertain whether it releases the drug in a predetermined manner (15). According to the theoretical release pattern, once-daily Metformin HCl SR formulation should release 175.6 mg in one hour and 46.3 mg per hour in 1, 2, 4, 6 and 8 hours, respectively. The average drug release from formulation (F5) simulates the theoretical drug release profile. All the formulations showed the burst release (175.6 mg) of Metformin HCl in the initial hours, which is probably due to faster dissolution of the highly water soluble drug from the superficial layers of matrix and its diffusion out of the matrix which leads to the entry of dissolution media through the pores.

**Analysis of release data**

The kinetics parameters for Metformin HCl release from the HPMC K4M and SCMC matrix tablets (F1 to F5) are shown, in table 4. The *in vitro* release profiles of drug from all the formulations could be best expressed by Higuchi’s equation as the plots showed high linearity (r² 0.99-0.99). Release of the drug from the matrix tablets containing hydrophilic polymers generally involves factors of diffusion. Diffusion is related to transport of drug from the dosage matrix into the *in vitro* study fluid, depending upon the concentration. As gradient varies, the drug released, and the distance for diffusion increases. This could explain why the drug diffuses at a comparatively slower rate as the distance from diffusion increases, which is referred to as square root kinetics or Higuchi kinetics. To confirm the diffusion mechanism, the data was fitted into korsmeyer’s equation (13). For matrix tablets an (n) value of near 0.5 indicates diffusion control and an n values of near 1.0 indicate erosion or relaxation control. Intermediate values suggest that diffusion and erosion contribute to the overall release mechanism. The formulations showed good linearity with the slope (n) ranging from 0.43 to 0.56 indicating that the diffusion is the dominant mechanism of drug release from these formulations.

The stability of Glimepride and Metformin HCl in these bilayer tablets was evaluated over three months at 25°C/60% RH and 40°C/75% RH for the best formulation among the prepared formulations (F4 and F5) and it was found that there is no significant difference in dissolution profile of initial and stability study samples as shown in figure 5 and 6.
Table 4 The correlation co-efficient values for different formulations.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi</th>
<th>(n) Value</th>
<th>Order of release</th>
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<tbody>
<tr>
<td>F1</td>
<td>0.93</td>
<td>0.99</td>
<td>0.99</td>
<td>0.43</td>
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<td>F2</td>
<td>0.93</td>
<td>0.98</td>
<td>0.99</td>
<td>0.53</td>
<td>non-Fickian</td>
</tr>
<tr>
<td>F3</td>
<td>0.99</td>
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<td>0.54</td>
<td>non-Fickian</td>
</tr>
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<td>F4</td>
<td>0.99</td>
<td>0.94</td>
<td>0.99</td>
<td>0.57</td>
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<tr>
<td>F5</td>
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<td>0.93</td>
<td>0.99</td>
<td>0.55</td>
<td>non-Fickian</td>
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</table>

Fig. 5 *In vitro* release profile of Metformin HCl from the bilayer matrix tablets (F4) after stability studies (bars represent ±SD (n=3)).

Fig. 6 *In vitro* release profile of Metformin HCl from the bilayer matrix tablets (F5) after stability studies (bars represent ±SD (n=3)).
Conclusion

The present study was carried out to develop a bilayered matrix tablets containing 1mg of Glimepride as immediate release component and 500mg Metformin HCl as sustained release component. The optimized ratios of super disintegrant SSG and hydrophilic polymers HPMC K4M and SCMC gave the desired release rate (zero order release/linear kinetics) matching with the theoretical release rates/rate calculated based on the pharmacokinetic properties of the drug. The hydrophilic polymers controlled the release of Metformin HCl for up to 8hrs intended for once daily administration, Glimepride as immediate release and Metformin HCl as sustained release indicate promising potential of both drugs in the form of bilayer tablets an alternative to the conventional dosage form.

Acknowledgement

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