FORMULATION AND PROCESS OPTIMIZATION OF GLIMEPIRIDE TABLETS

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Summary. Glimepiride is an effective antidiabetic drug, but its low aqueous solubility and slow dissolution rate might lead to low oral bioavailability. In this study, the possibilities for optimization of production process for glimepiride tablets are explored. Direct compression and tableting after granulation in a fluidized bed are examined as suitable and simplified methods for preparation of glimepiride tablets. Amaryl (glimepiride) 2 mg was used as a reference drug. The release profiles of tablets, produced by tableting after wet granulation in a fluidized bed can be considered to be similar with the reference drug, while the method of direct compression and tableting after granulation of excipients and subsequent powdering with the drug substance showed unsatisfactory results.

Key words: glimepiride, tablets, fluidized bed granulation.

Introduction

Glimepiride is a second generation sulfonylurea antidiabetic drug, indicated for the treatment of type 2 diabetes mellitus. Its mechanism of action includes stimulation of pancreatic β-cells to produce more insulin and thus lower the blood glucose level[1]. Glimepiride is an effective long acting antidiabetic drug with highly protein binding capacity. Concomitant use with insulin is an advantage for the clinical practice. However, the disadvantage for its use as oral dosage forms is mainly due to its low aqueous solubility (1.6 μg/mL) and slow dissolution rate, which lead to low oral bioavailability[2, 3].

According to Biopharmaceutical Classification system (BCS) Glimepiride belongs to a class II - drugs with low water solubility and high permeability. Various technological approaches to enhance the bioavailability of Glimepiride following oral administration have been proposed. Rajera et all. suggested the incorporation of Glimepiride in a solid dispersion of polymeric carrier. The authors proposed the modified gum Karaya as a suitable carrier [4]. The results from the study indicated that the optimum ratio of active substance to polymer was 1: 4.

Gupta et all. proposed different approach to increase the dissolution rate of Glimepiride and to improve its oral bioavailability by inclusion in a solid dispersion with Poloxamer 188 and subsequent tableting [5]. Tablets have been prepared by the method of direct tableting using various concentrations of Croscarmellose Sodium as disintegrant. Best results have been
achieved with a solid dispersion in which the ratio of drug to polymer was 1:4, and the amount of the disintegrant was 5%.

There are some reports on the incorporation of Glimepiride in microparticles by its dissolving in a different hydrophilic carriers matrix (Gelucire 50/13; Poloxamer 188 and PEG) [6]. Microparticles, developed by using these types of polymeric carriers exhibit a higher dissolution rate compared to the pure drug substance.

There are reports on incorporation of Glimepiride in Cellulose Acetate microparticles by the method of solvent evaporation[7]. These microparticles followed zero-order kinetics drug release.

Despite of the multiple approaches proposed to ensure an appropriate rate of Glimepiride release, one of the most widely used methods for preparation of Glimepiride tablets is described in patent EP 1928421 A2 [8]. This method consists of mixing of the active substance and excipients with a defined particle size, and subsequent tableting following wet granulating. The method provides high speed and rate of drug release in accordance with the requirements of European Pharmacopoeia. At the same time, this method requires the use of high-speed mixer granulator, and is associated with higher losses of production (material adhering to the granulator’s walls).

Therefore development of advanced technology for the production of tablets is linked, if possible, with simplification of the process and reduce the number of used machines. In operating conditions the development of simplified technologies most often associated with the method of direct compression tableting after granulation in a fluidized bed.

The aim of this study was to explore the possibilities for optimize the preparation of Glimepiride tablets compared to the currently used technology by tableting following wet granulation with fast moving mixer granulator. The preparation of Glimepiride tablets by direct compression method and tableting after granulation in a fluidised bed were examined.

### Materials and methods

Glimepiride was purchased from Indoco Remedies Ltd. Lactose monohydrate, Sodium starch glycolate, PVP, Microcrystalline cellulose and Magnesium stearate were obtained by BASF (Germany) and meet the requirements of the European Pharmacopoeia (PhEur).

**Qualitative and quantitative composition used in the study is given in Table 1.**

<table>
<thead>
<tr>
<th>Composition</th>
<th>Quantity (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active substance</td>
<td></td>
</tr>
<tr>
<td>Glimepiride</td>
<td>2.00</td>
</tr>
<tr>
<td>Excipients (intragranular)</td>
<td></td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>147.12</td>
</tr>
<tr>
<td>Sodium Starch Glycolate</td>
<td>9.30</td>
</tr>
<tr>
<td>PVP</td>
<td>0.90</td>
</tr>
<tr>
<td>Microcrystalline Cellulose(CC)</td>
<td>0.53</td>
</tr>
<tr>
<td>Excipients (extragranular)</td>
<td></td>
</tr>
<tr>
<td>Sodium Starch Glycolate</td>
<td>9.30</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.85</td>
</tr>
<tr>
<td>Total :</td>
<td>170.00</td>
</tr>
</tbody>
</table>

*Table 1: Qualitative and quantitative composition of Glimepiride (one tablet).*

**Physical chemical properties of Glimepiride:**

Glimepiride (Mw 490 g/mol) is practically insoluble in water. Glimepiride (2 mg) creates a saturated solution in 40 l of 0.1 M HCL dissolution medium (pH =1.2), 8.7 l acetate buffer medium (pH 4.5), and in 0,470 l phosphate buffer (pH = 7.5).

Obviously, the saturation of the dissolution medium at 900 ml phosphate buffer is far from ideal sink-conditions. Nevertheless the Generic department to FDA suggested the use of this media, so in the pilot studies a phosphate buffer, pH=7.5 was used.

**Granulation and mixing:**

1. Fast speed mixer granulator "Oystar Huttlin Mycromix";
2. An fluidized bed apparatus "Huttlin Unilab", provided with sprayer 1.2 mm.
**Drying:** fluidised bed apparatus "Huttlin Unilab". Supply air temperature: 45-55 °C. Residual moisture of the product ≤ 3.0%.

**Measurement of residual moisture:** Scale "Precisa XM 50" in 105°C.

**Calibration of the finished granules:** sieves with a pore size of 1.5 mm.

**Characterization of the finished granules:**
- Tapping apparatus: "Sotax TD1", equipped with a measuring cylinder of 250 ml. Samples volume - 100 ml was used in the study. The determination was made according to the requirements of European Pharmacopoeia. The following indicators were monitored: bulk volume, volume after tapping, index of compression and Hausner’s factor.

**Tableting:**
- The tablets were prepared using a rotary tablet machine "Kilian Pressima", equipped with punches (dimensions 11/6 mm). The mechanical strength of the tablets was with in the range 70-120 N. The measurement was conducted by using the apparatus for measuring of the mechanical strength "Sotax HT1". Ten tablets were used in the study.

**Drug release study:**
- The study was carried out by using the "Sotax AT7 Smart" apparatus, equipped with 7 vessels (apparatus type II - Paddle method), at speed of 50 rpm. The samples were analyzed by HPLC method - apparatus "Agilent G 1314F", at a wavelength of 228 nm.

**Factor of similarity:**
- The calculation of the factor of similarity was made according to the requirements of Guideline on the investigation of bioequivalence (CPMP / EWP / QWP / 1401/98 / Rev1).

**Results and discussion**
- Glimepiride tablets (comparative composition) were prepared by the method of tableting after wet granulation using a high speed mixer granulator. The active substance and the excipients were mixed until an uniform powder mixture was obtained. The uniformity of the powder was determined by analysis of three samples taken from different points in the mixer.
- The finished mixture was wetted with distilled (purified) water and was granulated using mixer granulator’s high-shear chopper. Drying takes place in an fluidized bed-type dryer at a temperature of 50°C until a residual moisture below 3%. The granules were calibrated through a sieve with a porosity of 1 mm. The granules are characterized by good flowability (index of compression 13.00 and factor of Hausner1.15) (Figure 1). Tablets having a mechanical strength of about 90 N were prepared after powdering with 1% of magnesium stearate.

![Figure 1: Carr’s index and Hausner’s ratio of direct compression mixture and granules, obtained by different methods.](image-url)
The dissolution test of the tablets was conducted after achieving the normal values of the quantitative content (95 ÷ 105%) and uniformity of content (85 ÷ 115%). The drug release profile of the tablets was compared to the release profile of the original medicinal product Amaryl 2 mg (glimepiride). The results are presented in Fig. 2.

It was found that both compositions released more than 85% of the active substance within 15th minute, i.e. both release profiles were considered as similar.

Subsequent experiments were aimed at exploring the possibility of producing Glimepiride tablets by the method of direct compression. Lactose # 200 and MCC (Avicel PH 101) used in the previous composition were replaced with Tabletose 80 and MCC (Avicel PH 102) – excipients developed for direct tabletting. By using titration of the ingredients uniformity, a complex powder characterized by good indicators of flowability was obtained (index of compression 15.7 and Hausner factor of 1.19). Tablets with mechanical strength 70-80 N were obtained by using direct tableting method. The produced tablets met the requirements for uniformity of the active substance content.

Figure 3 represents the results for the release rate and speed. The incorporated drug was released to approximately 75% for 15 min, after that the process slows sharply and drug release reached 82% after 60 min.

Analysing the obtained data it was assumed, that the binder excipient (PVP), used for direct tableting, helped to reduce the number of pores formed during tableting, thus negatively affecting the release process.

In order to minimize the influence of binder excipient used in the direct compression, a composition (wetted with a PVP solution) of Lactose, MCC, half of Sodium Starch Glycolate was prepared. Dried granules were then powdered with Glimepiride, Sodium Starch Glycolate and Magnesium stearate (Experiment 3). Dissolution test of the tablets obtained from this mixture was performed; the results are shown in Figure 3.

**Figure 2**: Release profiles of Amaryl 2 mg tablets and Glimepiride 2 mg tablets, produced by the method of tableting after wet granulation. The study was conducted in phosphate buffer, pH = 7.5.
In the time interval from 0 – 10 min a higher drug release rate of tablets prepared by granulated excipients was observed (approximately 73% compared to 35% drug release from the tablets prepared by direct tableting); after 15 min, 80% of the drug release was achieved and the process slows sharply. Nevertheless, it should be noted, that in the time interval 0-15 min almost 100% of the entrapped drug substance was released in the samples prepared by the method of tableting after wet granulation (Figure 1).

The similarity factor (f2) calculated for the tablets produced by the method of tableting after wet granulation was 37.48%; it did not meet the requirement for f2 (range 50 - 100).

The next series of experiments were aimed to investigate the possibility of producing the granules in a fluidised bed granulator. Possible positive result would allow to avoid wet granulation stage in mixer granulator and would reduce production losses. For this purpose, Hüttlin apparatus equipped with 1.2 mm sprayers was used.

In preliminary experiments the following granulation conditions were obtained:

- Flow speed – 280 m³/h
- Inlet air temperature – 50 ± 50°C
- Temperature of the granules– 32 ÷ 360°C

In preheated camera of the device homogenized mixture of Glimepiride, Lactose, MCC and half of Sodium Starch Glycolate is transferred to.

After reaching the operating temperature (38°C) a solution of PVP in distilled water was inflowing through the sprayer. The described parameters were not changed during inflowing of granulation solution. The granules were dried to residual moisture below 3% and were calibrated through a sieve of 1 mm. Finished granules characterizes with excellent flowability (index of compression 10, Hausner factor 1.11). However, the flow rate was lower than that of the granules obtained in a mixer-granulator (4.3 versus 5.4 g/s). This is probably due to the smaller average particle size, prepared under the conditions of fluidized bed granulator (Table 2).
Tablets with a mechanical strength of about 90 N were easily obtained after powdering with the rest of Sodium Starch Glycolate and Magnesium stearate from the granules.

The main concern in the development of this method was the ability of the micronized substance Glimepiride to pass through the pores of the filter and the impact of these losses on the quantitative content of active substance in the tablets. The result analyzes showed that the quantification of the active substance is about 98% (at the rate of 95 ÷ 105%, the test was carried out on 20 tablets). The uniformity of the content was also within the range of requirements (85 ÷ 115%, the test was carried out on 10 tablets).

Once we were convinced that the granules prepared in a fluidized bed can be used for production of tablets, complying with the requirements for mechanical strength, quantitative content and uniformity of content, a test to study the rate and speed of release was conducted.

The test results are presented in Figure 4.

Table 2: Sieve Analysis of granules with Glimepiride, prepared in a mixer granulator and drier in a fluidized bed.

<table>
<thead>
<tr>
<th>Sieve size (mm)</th>
<th>High-speed mixer granulator</th>
<th>Fluidized bed granulator</th>
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<tbody>
<tr>
<td>0.71</td>
<td>4.4</td>
<td>-</td>
</tr>
<tr>
<td>0.30</td>
<td>70.74</td>
<td>-</td>
</tr>
<tr>
<td>0.1</td>
<td>4.32</td>
<td>22.11</td>
</tr>
<tr>
<td>0.05</td>
<td>17.98</td>
<td>55.44</td>
</tr>
<tr>
<td>receiver</td>
<td>-</td>
<td>17.98</td>
</tr>
</tbody>
</table>

Figure 4: Release profile of Glimepiride 2 mg tablet, prepared by tableting after granulation in a mixer granulator and granulation in the fluidized bed. The study was conducted in an phosphate buffer medium, pH = 7.5.

The comparison between the release profiles of tablets prepared using tableting after wet granulation method, showed that over 85% of active substance was released at 15 min in both cases, i.e. release profiles are similar.
In order to confirm the suitability of the technological process of tablets preparation after granulation in a fluidised bed, the process of release into the medium with pH = 1.2 and pH = 4.5 need to be examined. As a result, the release profiles in these mediums should be similar to the release profiles of the tablets prepared after wet granulation.

Preliminary studies (Table 3) showed that 2 mg of Glimepiride give saturated solution in \(\approx 42\) L 0.1 M HCL, respectively in \(\approx 9\) L acetate buffer (pH = 4.5) which means that addition of 0.5% Sodium Lauryl Sulphate is required.

<table>
<thead>
<tr>
<th>Medium</th>
<th>Quantity (for 2 mg of Glimepiride)</th>
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</thead>
<tbody>
<tr>
<td>0.1 M HCL</td>
<td>(\approx 42) L</td>
</tr>
<tr>
<td>0.1 M HCL + 0.5 % Sodium Lauryl Sulphate</td>
<td>(\approx 60) ml</td>
</tr>
<tr>
<td>Acetate buffer (pH=4.5)</td>
<td>(\approx 9) L</td>
</tr>
<tr>
<td>Acetate buffer (pH=4.5) + 0.5 % Sodium Lauryl Sulphate</td>
<td>(\approx 100) ml</td>
</tr>
</tbody>
</table>

**Table 3:** Preliminary studies on the solubility of Glimepiride in different mediums.

The concentration of 2 mg Glimepiride dissolved in these mediums was 15, respectively 9 times, lower than the concentration of saturated solution, i.e. sink conditions are provided.

Initially, a comparative dissolution test in an acetate buffer medium (pH = 4.5) was carried out. The release profiles of the two types of tablets are presented in Figure 5.

**Figure 5:** The release profile of Glimepiride 2 mg tablets, prepared by tableting after granulation in a mixer granulator and granulating in the fluidized bed. The study was conducted in an acetate buffer medium, pH = 4.5.
Analysis of the results showed that both of the tablets released more than 85% of the active ingredient within 15th min, i.e. release profiles can be considered to be similar. The drug release in a medium with pH = 1.2 (0.1 M HCL + 0.5% Sodium Lauryl Sulphate) is presented in Figure 6.

Figure 6: Release profile of Glimepiride 2 mg tablets prepared by tableting after granulation in a mixer granulator and granulation in fluidized bed. The study was conducted in 0.1 M HCL + 0.5% Sodium Lauryl Sulphate, pH = 1.2.

The release profiles showed a lower rate of drug release in pH = 1.2 medium (72% vs 75% of the Glimepiride at 15 min).

The calculated factor of similarity had a value of 61.60 (acceptable values are in the range 50 ÷ 100), i.e. release profiles in an medium with pH = 1.2 can be also considered to be similar.

Conclusion

It was found that the direct tableting method was unsuitable for the preparation of Glimepiride 2 mg tablets. Although the powder mixture had good flow ability and the tablets had a good mechanical properties, the rate and speed of drug release are non conforming (f2 = 37.48). The study results showed that the method of tableting after granulation in a fluidised bed was much promising. The granules produced by this method showed a good flow ability and allowed preparation of tablets with good mechanical properties. The suitability of this technology for preparation of tablets Glimepiride 2 mg has also been demonstrated by comparison of the release profiles at the three media (pH = 1.2; pH = 4.5; pH = 7.5). In this case the similarity factor met predetermined criteria and was in the range of 50 ÷ 100.

References:


