Preparation of Rapidly Disintegrating Glipizide Tablets by Surface Solid Dispersion through Superdisintegrants

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ABSTRACT: The objective of this investigation was to enhance the dissolution of glipizide using solid dispersions containing different superdisintegrants and to prepare rapidly disintegrating glipizide tablets with rapid absorption through the oral cavity by direct compression of the prepared solid dispersion. Primojel, Ac-Di-Sol and Kollidon CL were used as superdisintegrants. These excipients were used in different ratios and by using solvent evaporation method, rapidly disintegrating glipizide tablets were prepared by direct compression of the prepared solid dispersion, as well as, by camphor sublimation method aiming for more enhancing of tablet disintegration. Glipizide loaded with Kollidon CL showed the best dissolution properties compared to the other tested excipients. The physical properties of all the prepared GZ tablet formulations were found to be acceptable according to USP/NF2002. Kollidon CL containing formulations showed the most rapid disintegration time values reaching one second in tablets prepared by camphor sublimation method. The most effective formula in decreasing the blood glucose level was that containing glipizide loaded with Kollidon CL, with significant difference from the physically mixed ingredients or the pure GZ powder depending on Student’s T-test for area above the blood glucose level.

KEYWORDS: Glipizide- superdisintegrants- Primojel- Ac-Di-Sol- Kollidon CL.

Introduction

Oral administration of glipizide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. Blood sugar control persists in some patients for up to 24 hours after a single dose of glipizide. Gastrointestinal absorption of glipizide in man is uniform, rapid, and essentially complete. Peak plasma concentrations occur 1-3 hours after a single oral dose. The half-life of elimination ranges from 2-4 hours in normal subjects, whether given intravenously or orally. Many formulations of glipizide was developed and evaluated for extending the release (Chung et.al, 2002, Hsieh et.al, 2006, and Jamzad et.al.,2006), or for enhancing solubility (Gan et.al.2002, and Aly et.al.2003).

With the increase in the average human life, drug administration for elderly patients has become more important. Due to a decline in swallowing ability with age, a great many elderly patients complain that it is difficult to take medication in the form of tablets (Mallet, 1996). Recently, useful dosage forms, such as rapidly disintegrating or dissolving tablets have been developed and applied clinically (Sugihara, 1995, Ishikawa et.al. 1999, and Sallam et.al., 1998). This dosage form can be used also for children instead of syrup, as well as, for local action within oral cavity as well as local anesthetics for toothache, cold sore, or teething product. Camphor sublimation method (Koizumi et.al., 1997) has proved to be effective for the production of tablets of higher porosity. Thus, the objective of this investigation was the enhancement of dissolution and consequently rapid hypoglycemic effect of glipizide by preparing solid dispersion containing Primojel, Ac-Di-Sol or Kollidon CL as superdisintegrants, in different ratios, using a solvent evaporation method. Also, the objective is to prepare rapidly disintegrating glipizide tablets with rapid absorption through the oral cavity by direct compression of the prepared solid dispersion, as well as, by camphor sublimation method aiming for more enhancing of tablet disintegration. The influence of three tablet formulations, containing GZ-KollidonCL (1:9) loaded and physical mixture, as well as pure GZ powder on blood glucose level of mice was, also studied.

Experimental

Materials

Primojel and Kollidon CL were obtained from Avebe, Netherlands). Glipizide, Ac-Di-Sol, Direct compression sugar, Aspartam and Tutti Fruitti: were obtained as gifts, from Dar Al-Dawa Pharmaceutical Manufacturing Co. Ltd., Amman, Jordan. Polyethylene glycol PEG6000 was obtained from Panreac Quimica, SA, Spain. All other chemicals employed were of analytical reagent grade.

Method

Preparation of surface solid dispersion by solvent evaporation method

The specified amount of GZ was dissolved in the least amount of methanol: dichloromethane (1:3) at room
temperature and thoroughly mixed, in a mortar, with each exceptient; Kollidon CL, Ac-Di-Sol or Primojel (the latter two have been proved to be highly water adsorbant) (20) in GZ: Excepient 1:1, 1:3, 1:6 and 1:9 ratios. Then the solvents were evaporated an oven at 80°C, for two hours and the product obtained was powdered in a mortar and passed through a 250μm sieve, and stored in a desicator containing CaCl₂ over night. Five grams were prepared for each formula.

**Differential Scanning Calorimetry (DSC) Studies**

Ten mg of the pure GZ powder, Kollidon CL and GZ-Kollidon CL surface solid dispersion, were subjected to DSC studies using Perkin Elmer DSC7 Model. The scanning rate was 10°/min.

**Flowability of Powder**

*Bulk density:* of mixed powders before compression was studied by determining the Hausner’s factor (equation 1) and the Carr’s Index from the fluffy and tapped bulk densities of a known weight of sample using a measuring cylinder (equation 2).

\[
\text{Hausner’s factor} = \frac{D_f}{D_t} \quad \text{...(1)}
\]

\[
\text{Carr’s Index} = \frac{D_t - D_o}{D_o} \times 100 \quad \text{...(2)}
\]

Where: 
- \(D_f\) (fluffy density) = \(\frac{\text{Weight}}{V(\text{fluffy volume})}\)
- \(D_t\) (tapped density) = \(\frac{\text{Weight}}{V(\text{tapped volume})}\)

**Dissolution Studies**

A USP/NF2002 Hanson Dissolution Apparatus II (paddle) with six cups was employed for this purpose. Amount of each of the prepared surface solid dispersion equivalent to 5mg GZ was placed in each vessel, rotating at 100 r/min. in 900 ml of the dissolution medium for GZ (Phosphate buffer, pH = 7.4, prepared according to USP/NF2002 procedures) at 37°C. The experiment was run for 1 hour during which samples were withdrawn at suitable time intervals, and replaced by equal volume of dissolution medium kept at 37°C. Samples were assayed spectrophotometrically at 275.3 nm for GZ.

**Preparation of Tablets**

Surface solid dispersion containing GZ with Kollidon CL, Ac-Di-Sol or Primojel in 1:9 ratios were chosen for tablet preparations according to the formulas presented in Table 1. The ingredients were thoroughly mixed in a cubic mixer (Erweka, Germany) for 5 min. Two hundred flat-faced 100mg tablets with 8 mm diameter were prepared at constant rate, by direct compression using Double-Punch Tablet Machine (Erweka, AR400E, Germany). The machine was adjusted to produce tablets of 40-45 Newton hardness, in all cases. Another GZ tablet formulations were prepared containing 20% powdered camphor. The ingredients were thoroughly mixed and compressed into 120 mg tablets as above. GZ tablets (containing camphor) were then placed in an oven at 80°C for 30 min to eliminate camphor by sublimation (Koizumi et.al., 1997).

Table 1. Constituents of glipizide tablets containing solid dispersion of glipizide with Kollidon CL, Ac-Di-Sol or Primojel (1:9).

<table>
<thead>
<tr>
<th>Materials (mg)</th>
<th>Concentration (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glipizide-excipient (1:9)</td>
<td>50</td>
</tr>
<tr>
<td>Direct compression sugar</td>
<td>43</td>
</tr>
<tr>
<td>PEG6000</td>
<td>1.5</td>
</tr>
<tr>
<td>Aspartame</td>
<td>5</td>
</tr>
<tr>
<td>Totti frutti</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**Evaluation of the prepared tablets**

**Uniformity of Weight**

Twenty tablets taken randomly were weighed individually and the average weight, the standard deviation, and the coefficient of variation percent, C.V. %, were calculated.

**Uniformity of Thickness and Diameter**

The thickness and diameter were determined, from random samples of ten tablets, using and Erweka TBH 50 Hardness Tester.

**Measurement of Wetting Time and Water Absorption Ratio**

Procedures similar to those of Bi et.al.,1996, were used to measure tablet wetting time and water absorption ratio. A piece of paper tissue folded twice was placed in a small culture dish (i.d. = 6.5 cm) containing 6 ml of water. A tablet to be tested was put on the paper, and the time for complete wetting was measured. The results obtained were the average of five determinations.

**Disintegration time (in vitro)**

The disintegration time for 6 tablets, in distilled water at 37°C, was determined using Pharma Test apparatus, Italy.

**Dissolution Studies**

A USP/NF2002 Hanson Dissolution Apparatus with six cups was employed for this purpose. One tablet was placed in each basket and the same procedures mentioned above were utilized except that apparatus I was used, i.e., the rotating paddles were replaced by baskets.
In vivo study of glipizide

A method similar to that applied before (Aly et al., 2003, Martin et al., 1983) was performed. Five groups of mice were fasted (with free water) at least 12 hours before the experiment. Each group consists of five mice weighing 16-20 grams each. Before drug administration, a blood control samples from each mouse of the three groups were taken, from behind the eyeball through the angle of ocular cavity using small capillary tubes. The blood glucose level was determined using the glucose-measuring instrument (SURESTEP “LIFESCAN, Inc.”, Johnson-Johnson Company, Milpitas, California, USA). The instrument was self-calibrated; just read the result keeping samples well dried before reading to avoid contaminating the lens. The different formulas of glipizide were administered orally to each group of mice using stomach intubations technique. A dose of 1 mg/0.5ml was administered in suspension form for each mouse (freshly prepared for each time interval), blood samples were collected, and the determination of glucose was performed immediately. Samples were withdrawn at 0.5, 1, 2, 3, 4 and 5 hours. All in-vivo experiments were started at 8:00 am.

Data analysis

The student t-test was applied as the statistical method of analysis (SPSS computer program), where, p<0.05 was considered as the least level of significance.

Results and discussions

Dissolution of powder

The dissolution rate study of GZ from the prepared solid dispersions containing different GZ: excipient ratios (1:1, 1:3, 1:6, and 1:9) in comparison with the physical mixture and drug alone were studied. It could be observed that rapid dissolution rate could be obtained by increasing any of the tested disintegrant concentration (Fig 1-3). Formulas containing (1:9) drug: excipient ratio shows the highest dissolution rate (Fig 4). The three tested disintegrants; Primojel, Ac-Di-Sol and Kollidon CL, revealed pronounced improvement of dissolution rate compared to the untreated GZ powder. The latter showed non-wetable hydrophobic properties with less than 1% dissolution through one hour. Whereas, pronounced enhancement of dissolution rate in all the tested formulations, reaching 80-90% through one hour in formulations containing 1:9 (GZ:disintegrant) ratios. Kollidon CL containing Formula showed the most rapid dissolution properties compared to the other tested excipients (Fig. 4). Also, the physical mixing of GZ with any of the tested disintegrant could not affect the rate of dissolution. Thus, the effect of any disintegrant used is only through solid dispersion, which performs very fine dispersion of drug molecules throughout the rapid disintegrating material resulting in the pronounced rapid dissolution of the drug.

![Fig. 1 Release profiles of GZ-AcDiSol (AC) from solid dispersion powder at different ratios, pure GZ and physical mixture.](image-url)
Fig. 2 Release profile of GZ-Primojel (PR) from solid dispersion powder at different ratios, pure GZ and physical mixture.

Fig. 3 Release profile of GZ-KollidonCL (KL) from solid dispersion powder at different ratios, pure GZ and physical mixture.
Fig. 4 Release profiles of GZ Different excipients from solid dispersion powder at (1:9) ratio and pure GZ.

Table 2. Flowability properties of Glipizide tablet ingredients before compression.

<table>
<thead>
<tr>
<th>Properties</th>
<th>Carr’s index</th>
<th>Hausner’s factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glipizide powder</td>
<td>34.310</td>
<td>1.545</td>
</tr>
<tr>
<td>Glipizide and Primojel</td>
<td>8.000</td>
<td>1.087</td>
</tr>
<tr>
<td>Glipizide, Primojel and Camphor</td>
<td>13.333</td>
<td>1.154</td>
</tr>
<tr>
<td>Glipizide and AC-Di-Sol</td>
<td>17.647</td>
<td>1.214</td>
</tr>
<tr>
<td>Glipizide, AC-Di-Sol and Camphor</td>
<td>25.000</td>
<td>1.333</td>
</tr>
<tr>
<td>Glipizide and Kollidon CL</td>
<td>19.048</td>
<td>1.235</td>
</tr>
<tr>
<td>Glipizide, Kollidon CL and Camphor</td>
<td>18.182</td>
<td>1.222</td>
</tr>
</tbody>
</table>

**Powder flowability**

The inclusion of loaded drug-excipient in all formulations pronouncedly improves the flowability compared to the nonflowable Glipizide powder (Hausner’s Factor is 1.52) as shown in Table 2. Primojel’s inclusion revealed the best flowability (Hausner’s Factor of 1.09), followed by those containing AcDiSol and Kollidon, with Hausner’s Factor of 1.21 and 1.24, respectively. Also, it could be observed that the inclusion of camphor slightly decreases the flowability. Thus, as a result, those mixtures may produce good compressability properties due to decreasing of Carr’s Index values, compared to the nonflowable and noncompressable untreated powdered drug.

**DSC Study**

To study the physicochemical properties of the pure GZ powder, KollidonCL and GZ- KollidonCL solid dispersion, DSC were performed. The results presented in Fig 5 revealed that; the broad peak of KollidonCL at about 75°C showed similar sharpness when loaded with GZ. The latter revealed melting point at 210°C (Fig 5, B), that has showed a very low intensity, or disappearance of peak...
when dispersed with KollidonCL as shown in Fig.5, C, indicating decreasing in its crystallinity and confirming that solid dispersion is obtained.

**Gilipizide tablets from solid dispersion**

**Physical properties:**

Table 3 revealed that; all the prepared tablet formulations showed acceptable physical properties according to the USP/NF2002. The uniformity of weight fulfills the requirement with less than ±5% in all cases. Also, all the tested formulations showed acceptable drug content values with less than ±15% deviation, i.e. fulfill USP/NF2002 requirements. The uniformity of thickness and diameter as well as the hardness values are acceptable.

The loss in weight after camphor sublimation at 80°C for 30 min was equivalent to about 20%; i.e. all camphor has been removed.

**Table 3. Physical properties of the prepared Gilipizide tablets.**

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of Weight (mg)</td>
<td>Mean</td>
<td>0.10232</td>
<td>0.10141</td>
<td>0.09219</td>
<td>0.09911</td>
<td>0.11114</td>
<td>0.09565</td>
</tr>
<tr>
<td></td>
<td>C. V.%</td>
<td>3.34693</td>
<td>4.16953</td>
<td>3.72262</td>
<td>3.62182</td>
<td>3.42203</td>
<td>3.62760</td>
</tr>
<tr>
<td>Uniformity of Diameter (mm)</td>
<td>Mean</td>
<td>8.10000</td>
<td>8.03333</td>
<td>8.18333</td>
<td>8.13333</td>
<td>8.16670</td>
<td>8.16667</td>
</tr>
<tr>
<td></td>
<td>C. V.%</td>
<td>1.06917</td>
<td>0.71869</td>
<td>0.35276</td>
<td>0.35493</td>
<td>0.33502</td>
<td>0.35348</td>
</tr>
<tr>
<td>Uniformity of Thickness (mm)</td>
<td>Mean</td>
<td>2.01667</td>
<td>2.03333</td>
<td>1.61667</td>
<td>2.06667</td>
<td>2.51667</td>
<td>2.46667</td>
</tr>
<tr>
<td></td>
<td>C. V.%</td>
<td>1.43145</td>
<td>2.83943</td>
<td>1.78562</td>
<td>1.39684</td>
<td>3.03482</td>
<td>1.17031</td>
</tr>
</tbody>
</table>

Fig. 5 Differential scanning calorimetry of loaded glipizide (GZ) with kollidon CL in comparison with pure GZ and kollidon CL.
Disintegration time values represented in Table 4; indicates that Kollidon CL containing formulations showed the most rapid disintegration time values reaching one second in tablets prepared by camphor sublimation method and five seconds for tablets containing GZ-Kollidon solid dispersion Primojel containing tablets with GZ revealed higher disintegration time values either with camphor (21 seconds), or without it (44 seconds). The wetting time values were directly proportional to the disintegration time values (the correlation coefficient \( r^2 \) was 0.998, Fig 6).

**Table 4.** Wetting and disintegration time results of the prepared Glipizide tablets.

<table>
<thead>
<tr>
<th>Properties</th>
<th>Formula</th>
<th>Glipizide &amp; Primojel</th>
<th>Glipizide, Primojel &amp; Camphor</th>
<th>Glipizide &amp; Ac-Di-Sol</th>
<th>Glipizide, Ac-Di-Sol &amp; Camphor</th>
<th>Glipizide &amp; Kollidon Cl</th>
<th>Glipizide, Kollidon Cl &amp; Camphor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wetting time (sec)</td>
<td>Mean</td>
<td>62.667</td>
<td>45.333</td>
<td>81.000</td>
<td>68.000</td>
<td>42.333</td>
<td>8.8333</td>
</tr>
<tr>
<td></td>
<td>C.V.%</td>
<td>3.32181</td>
<td>2.54713</td>
<td>2.13833</td>
<td>3.89081</td>
<td>3.60832</td>
<td>3.26800</td>
</tr>
<tr>
<td>Disintegration time (sec)</td>
<td>Mean</td>
<td>42.667</td>
<td>38.667</td>
<td>79.333</td>
<td>58.000</td>
<td>5.1667</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>C.V.%</td>
<td>5.89831</td>
<td>1.49315</td>
<td>1.92545</td>
<td>4.56164</td>
<td>5.58726</td>
<td>0</td>
</tr>
</tbody>
</table>

![Fig. 6 Correlation between wetting and distegration time for GZ-Excipients for different formula in presence of camphor.](image)
Dissolution of GZ tablets

The dissolution rate study of different tablet formulations (Fig.7) revealed that GZ release from all the prepared tablet formulations was very rapid, reaching 84% through 46 min. GZ including tablets showed initial very rapid dissolution through 2 min for Primojel tablets followed by pronounced very rapid dissolution of kollidonCL containing tablet (Fig.7). Fig.8 showed a photographic picture of each formula after one minute when in contact with water, the swelling and destruction of tablets containing Primojel, while, intact swelling of tablets of Kollidon CL. It could be observed from Fig 7 that through the first 20 min the amount dissolved in case of Kollidon CL was comparatively higher than that dissolved from the other two formulations.

Fig. 7 Release profiles of glipizide tablets prepared from different solid dispersion formulas with and without camphor.

Fig. 8 Photograph showing the effect of water on Glipizide tablets containing: AcDiSol (A), kollidon CL (B), and primojel (C), before hydration (the upper photos) and after hydration (the lower photos).
In vivo Study of Glipizide

Because the dissolution of a dosage form in vitro is often the rate-limiting factor when determining the physiological availability of a drug, measuring the in vitro dissolution rate or a related parameter is more likely to offer a meaningful indication of physiological availability (Aly et al., 2003, and 2005). Powdered GZ was administered to the mice in suspension form, the decrease in glucose level could be observed after 0.5 hours of administration as shown in Fig. 9. This effect was gradually enhanced until 6 hours. That observation reflects an increase in the blood level of GZ as a function of dissolution from the intestine. The in vivo study was performed for surface solid dispersion containing GZ with Kollidon CL, AcDiSol or Primojel formulations, it could be noticed that formulations containing glipizide: Kollidon CL (1:9) showed comparatively the lowest glucose level, while the other formulas showed closely similar results.

Table 5 revealed the area under the curve (AUC), area above the curve (AAC), and relative availability (RA) of each formula. It could be observed that the most effective formula in decreasing the blood glucose level was that containing glipizide and Kollidon CL prepared by surface solid dispersion technique, while the other two formulations showed closely similar results. Upon applying Student’s T-test (Independent or unpaired) for Area above the blood glucose level (AAC) for each of the tested formulation significant variations between results were observed, the Kollidon CL containing formula was significantly different from other two formulas Table 5 and Fig 8.

Table 5. In Vivo availability results for Glipizide after oral administration of 1 mg to mice.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Parameter</th>
<th>AUCa</th>
<th>AACb</th>
<th>Relative Availability</th>
<th>&quot;p&quot; value (For AAC data)</th>
<th>Significance (P&gt;0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GZ Free[A]</td>
<td>AUC</td>
<td>393.246</td>
<td>206.754</td>
<td>1.000</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>GZ:Kollidon (1:9) [B]</td>
<td>AAC</td>
<td>287.170</td>
<td>312.830</td>
<td>1.513</td>
<td>0.002 (3.016)c</td>
<td>S</td>
</tr>
<tr>
<td>GZ&amp;Kollidon(1:9) Physical Mixture[C]</td>
<td>AUC</td>
<td>399.463</td>
<td>200.537</td>
<td>0.970</td>
<td>0.881 (3.406)</td>
<td>NS</td>
</tr>
</tbody>
</table>

a: AUC means the area under the blood sugar curve.  b: AAC means the area above the blood sugar curve.  c: Values between parentheses represent the standard error.  S: Significant difference.  NS: Non-significant difference.
Conclusion

Kollidon containing formulations of glipizide showed the most rapid disintegration time values reaching one second in tablets prepared by camphor sublimation method with rapid dissolution rate. This formula also, was the most effective in decreasing the blood glucose level of mice.

References


