Introduction

The term diabetes mellitus DM describes a group of metabolic disorders characterized by chronic hyperglycemia with some disturbances of carbohydrates, fat and protein metabolism resulting from defect in insulin secretion, action or both [1]. Antidiabetic medications treat diabetes mellitus by lowering glucose levels in the blood of people with diabetes mellitus to keep the blood glucose level at or close to normal levels [2].

Metformin (MET), chemically, is 1,1-dimethyl biguanide (Fig. 1). It decreases the gluconeogenesis process and increases the glucose uptake by muscles and fat cells. It is the cornerstone for the treatment of Diabetes Mellitus type II, where it is used alone or in combination with other antidiabetic classes like sulfonylurea’s, alaphaglycosidase inhibitors, or insulin [3]. Our literature survey verified that determination of metformin has been carried out using HPLC in tablets [4-8], in human plasma [9,10] or through using capillary electrophoresis [11,12].

Gliclazide (GLC ), is a second generation sulphonylurea drug which is chemically, 1-(3-Azabicyclo[3.3.0] oct-3-yl)-3-(p-tolyl)sulfonyl)urea (Fig. 1). It increases insulin release from $\alpha$- cells through closure of $K^+$ (KATP) channels. This will lead to $\alpha$- cell membrane depolarization and calcium influx which in turn will cause insulin secretion [13]. The determination of gliclazide has been carried out using variant techniques but specifically through spectrophotometry [14-16], HPLC [17-20] and HPTLC [21].

Glimepiride (GLM) is another potent third generation sulfonylurea derivative and it is widely used in the treatment of non-insulin-dependent type II diabetes mellitus as an oral hypoglycemic agent due to its consistent secretagogue action [22]. Chemically, it is 1-{{p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamide) ethyl] phenyl} sulfonyl}-3-(trans-4-methylcyclohexyl) urea (Fig. 1). Many chromatographic [22-24] and spectrophotometric methods [25-31] were also reported for determination of glimepiride either alone or in combination with other antidiabetic drugs.

AN ISOCRATIC RP-HPLC method has been developed for rapid and simultaneous separation and estimation of three antidiabetics drugs, metformin, gliclazide and glimepiride in tablet dosage forms within 6 minutes. Separation was carried out on a Thermo Scientific® BDS Hypersil C8 column (5µm, 2.50 x 4.60 mm) using a mobile phase of MeOH : 0.025M KH$_2$PO$_4$ adjusted to pH 3.20 using ortho - phosphoric acid (70: 30, v/v) at ambient temperature. The flow rate was 1 mL/min and UV detection was set at 235 nm. The retention time of metformin, gliclazide and glimepiride was noted to be 3.06, 4.33 and 6.00 minutes respectively, indicating a very short analysis time rather than other reported methods. Also, limits of detection were reported to be 0.05, 1.21 and 0.11 µg/mL for metformin, gliclazide and glimepiride, respectively, showing a high degree of the method sensitivity. The method was then validated according to ICH guidelines where it was found to be accurate, reproducible and robust. Finally, the method was compared statistically with reference methods indicating that there is no significant difference between them in respect of precision and accuracy.

Keywords: RP-HPLC, Metformin, Gliclazide, Glimepiride, Tablets.
To the best of our knowledge and comprehensive survey, metformin, gliclazide and glimepiride mixture in dosage form was not determined before by RP-HPLC despite their synergistic action. As such, the present work introduces a simple, very rapid, reproducible and sensitive chromatographic method for the determination of the three antidiabetic drugs in tablets formulations. This method also has another advantage to protect analytical scientists and chemists from the exposure to volatile and corrosive organic solvents during experimentation using an environmentally benign mobile phase.

**Experimental**

**Apparatus**

- HPLC instrument (Germany) with a Thermo Scientific® BDS Hypersil C₈ column (5 µm, 2.50 x 4.60 mm), DAD absorbance detector, HPLC QUAT pumps and connected to PC computer loaded with Agilent 1200 HPLC.
- Labomed® Spectro UV-VIS Double Beam (UVD-2950) Spectrophotometer with matched 1 cm quartz cells and connected to windows compatible computer using UV Win 5 Software v6.
- HANNA®HI 8314 membrane pH-meter (Romania) for pH adjustment.

**Materials and reagents** All solvents and reagents were HPLC analytical grade (methanol, potassium dihydrogen phosphate and orthophosphoric acid were supported from Fisher Scientific, England).

**Metformin** (99%, Mina Pharm, Egypt), gliclazide (99%, Sigma, Egypt) and glimepiride (99%, GNP Pharm, Egypt) standard solutions of 200 µg/mL were prepared by dissolving 0.01 mg of each pure drug in 50-mL of the mobile phase.

**Glucophage®** tablets (Mina Pharm, Egypt) are labeled to contain 500 mg metformin, Gliclazide® tablets (Sigma, Egypt) are labeled to contain 80 mg gliclazide and Glaryl® tablets (GNP Pharm, Egypt) are labeled to contain 3 mg glimepiride.
Procedures

Preparation of standard calibration curves

Appropriate mixed dilutions of metformin, gliclazide and glimepiride standard stock solutions were done in 10-mL volumetric flasks to get final concentrations of 5, 12.50, 25, 50 and 100 µg/mL for all drugs. A 10 µL of each mixture was then injected into the column and the chromatogram was obtained at 235 nm. A graph was plotted as concentration of drugs against response (peak area). Regarding validation QC samples, concentrations of 25, 50 and 100 µg/mL were selected as low (LQC), medium (MQC) and high (HQC) levels, respectively.

Analysis of pharmaceutical tablets

5 tablets of Glucophage®, Gliclazide® and Glaryl® tablet formulations were weighed and powdered. An accurately weighed amounts of the powder equivalent to 20 mg of each drug were dissolved in methanol, filtered into 100-mL measuring flasks and completed to volume with the mobile phase. The procedure was then completed as mentioned above under the general procedure 2.3.1.

Results and Discussion

Optimization of Chromatographic Conditions

Spectroscopic analysis of the three drugs in the range of 200-400 nm showed that metformin, gliclazide and glimepiride have UV absorbance maxima (\(\bar{\lambda}_{\text{max}}\)) at 237, 228 and 229 nm, respectively as depicted in Fig. 2. Therefore, the chromatographic detection was performed at 235 nm as the appropriate wavelength using a DAD detector. The method was performed on a Thermo Scientific® BDS Hypersil C8 column (5 µm, 2.50 x 4.60 mm).

Furthermore, under several trials of mobile phase optimization regarding its composition ratio and pH, it was observed that the optimized mobile phase was determined as a mixture of MeOH : 0.025 M potassium dihydrogen phosphate adjusted to pH 3.20 using ortho-phosphoric acid (70: 30, v/v) at a flow rate of 1 mL/min. Under these conditions, metformin, gliclazide and glimepiride in pure form can be separated and eluted at 3.06, 4.33 and 6.00 minutes as illustrated in Fig. 3 A and in dosage form at 3.06, 4.17 and 5.97 minutes, respectively as illustrated in Fig. 3B. However, in both cases, the optimum mobile phase showed symmetrical peaks (0.62 < T < 1.13), capacity factor (1<k < 10), resolution > 2 and theoretical plates > 2000. Table 1 shows all system suitability parameters of the proposed RP-HPLC method for simultaneous determination of the three antidiabetic drugs in both pure and tablet formulation.

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![Fig. 2. Overlain spectra of 1 µg/mL. metformin (MET___), gliclazide (GLC__ _) and glimepiride (GLM.......)](image) at maximum wavelengths of 237, 228 and 229 nm, respectively.
Fig. 3. HPLC Chromatogram of (A) 2.5 µg/mL authentic mixture of metformin (MET), pioglitazone (PIO) and glimepiride (GLM) and (B) Glucophage®, Gliclazide® and Glaryl® tablets mixture using Thermo
Scientific® BDS Hypersil C8 column (5 µm, 2.50 x 4.60 mm) and a mobile phase of MeOH : 0.025 M
KH2PO4 adjusted to pH 3.20 using ortho - phosphoric acid (70: 30, v/v). Other chromatographic conditions
are stated in Results and Discussion section 3.1.

TABLE 1. System suitability parameters for metformin (MET), gliclazide (GLC) and glimepiride (GLM) in both
pure and dosage forms.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pure form</th>
<th>Dosage form</th>
<th>Reference values [33]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MET</td>
<td>GLC</td>
<td>GLM</td>
</tr>
<tr>
<td>Retention time, tr</td>
<td>3.06</td>
<td>4.33</td>
<td>6.00</td>
</tr>
<tr>
<td>Capacity factor, k’</td>
<td>1.36</td>
<td>2.34</td>
<td>3.62</td>
</tr>
<tr>
<td>Peak asymmetry (Tailing factor, T)</td>
<td>1.13</td>
<td>0.87</td>
<td>0.89</td>
</tr>
<tr>
<td>Therotical plates, N</td>
<td>5489</td>
<td>4640</td>
<td>4322</td>
</tr>
<tr>
<td>Resolution, Rs</td>
<td>---</td>
<td>5.99</td>
<td>5.40</td>
</tr>
<tr>
<td>Selectivity (Separation factor, a.)</td>
<td>1.71</td>
<td>1.55</td>
<td>1.55</td>
</tr>
</tbody>
</table>

*Egypt.J.Chem. 62, No. 3 (2019)*
Method Validation

The method validation was performed according to international conference of harmonization guidelines (ICH) [32].

Linearity

Five different concentrations of the drug mixture were specified for linearity studies. The calibration curves obtained by plotting peak area against concentration showed linearity in the concentration range of 5 - 100 µg/mL for all drugs (Table 2). Linear regression equations for metformin, gliclazide and glimepiride were found to be \( y = 66.46x + 68.94 \), \( y = 3.53x + 4.97 \) and \( y = 30.25x + 36.42 \), respectively and the regression coefficient values \( r \) were 0.999 for the three drugs indicating a high degree of linearity (Fig. 4).

Accuracy and precision

The accuracy of the method was determined by investigating the recoveries of metformin, gliclazide and glimepiride in pharmaceutical formulations at concentration levels covering the specified range (three replicates of each concentration). From the amount of the drug estimated, the percentage recovery of each tablet concentration was calculated and the results shown in Table 3 are indicating excellent recoveries for all drugs in their dosage forms.

The precision of the method was evaluated according to intra-day and inter-day precision using validation QC samples at concentrations of 25, 50 and 100 µg/mL. Intra-day precision was evaluated in respect of both standard deviation (SD) and coefficient of variation (CV%) regarding three replicate determinations using the same solution containing pure drugs on the first day of analysis. The SD and CV% values (varied from 0.14 to 2.39) revealed the high precision of the method. For inter-day reproducibility, the day-to-day SD and CV% values were also in the acceptable range of 0.07 - 1.99. These results shown in Table 4 indicate that the proposed method has an adequate precision to simultaneously determine the three drugs in both pure and pharmaceutical formulations.

Fig. 4. Calibration curves for authentic mixture of metformin (MET), gliclazide (GLC) and glimepiride (GLM) using the proposed HPLC method.
<table>
<thead>
<tr>
<th>Parameters</th>
<th>MET</th>
<th>GLC</th>
<th>GLM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Taken µg/mL</td>
<td>Found µg/mL</td>
<td>Recovery %</td>
</tr>
<tr>
<td>5</td>
<td>4.90</td>
<td>98.10</td>
<td>-1.89</td>
</tr>
<tr>
<td>12.50</td>
<td>12.35</td>
<td>98.81</td>
<td>-1.18</td>
</tr>
<tr>
<td>25</td>
<td>24.91</td>
<td>99.65</td>
<td>-0.34</td>
</tr>
<tr>
<td>50</td>
<td>50.56</td>
<td>101.10</td>
<td>1.13</td>
</tr>
<tr>
<td>100</td>
<td>99.76</td>
<td>99.76</td>
<td>-0.23</td>
</tr>
<tr>
<td>Mean</td>
<td>99.49</td>
<td>-0.50</td>
<td></td>
</tr>
<tr>
<td>±SD</td>
<td>1.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>±RSD</td>
<td>1.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>±SE</td>
<td>0.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variance</td>
<td>1.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOD (µg/mL)</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOQ (µg/mL)</td>
<td>0.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parameters</td>
<td>MET (Glucophage®)</td>
<td>GLC (Gliclazide®)</td>
<td>GLM (Glaryl®)</td>
</tr>
<tr>
<td>------------</td>
<td>------------------</td>
<td>------------------</td>
<td>---------------</td>
</tr>
<tr>
<td></td>
<td>Taken µg/mL</td>
<td>Found µg/mL</td>
<td>Recovery</td>
</tr>
<tr>
<td>5</td>
<td>4.98</td>
<td>99.61</td>
<td>-0.38</td>
</tr>
<tr>
<td>12.50</td>
<td>12.27</td>
<td>98.21</td>
<td>-1.78</td>
</tr>
<tr>
<td>25</td>
<td>24.95</td>
<td>99.83</td>
<td>-0.16</td>
</tr>
<tr>
<td>50</td>
<td>49.73</td>
<td>99.47</td>
<td>-0.52</td>
</tr>
<tr>
<td>100</td>
<td>100.18</td>
<td>100.18</td>
<td>0.18</td>
</tr>
<tr>
<td>Mean</td>
<td>99.46</td>
<td>-0.53</td>
<td></td>
</tr>
<tr>
<td>±SD</td>
<td>0.74</td>
<td>1.62</td>
<td></td>
</tr>
<tr>
<td>±RSD</td>
<td>0.75</td>
<td>1.62</td>
<td></td>
</tr>
<tr>
<td>±SE</td>
<td>0.33</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>Variance</td>
<td>0.55</td>
<td>2.65</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 4. Intra- & inter-day precision results using 3 quality control samples of metformin (MET), gliclazide (GLC) and glimepiride (GLM) using the proposed method.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Concentrations (µg mL)</th>
<th>Mean ± SD</th>
<th>CV (%)</th>
<th>Accuracy %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intra-day runs</strong>&lt;br&gt;(n=3)</td>
<td>MET</td>
<td>100</td>
<td>99.85 ± 0.24</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50</td>
<td>101.46 ± 0.16</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25</td>
<td>98.63 ± 0.25</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td>GLC</td>
<td>100</td>
<td>99.20 ± 0.38</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50</td>
<td>98.64 ± 2.01</td>
<td>2.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25</td>
<td>100.07 ± 2.38</td>
<td>2.39</td>
</tr>
<tr>
<td></td>
<td>GLM</td>
<td>100</td>
<td>99.75 ± 0.14</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50</td>
<td>100.66 ± 0.23</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25</td>
<td>98.29 ± 0.18</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Inter-day runs</strong>&lt;br&gt;(n=3)</td>
<td>MET</td>
<td>100</td>
<td>99.85 ± 0.07</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50</td>
<td>101.16 ± 0.08</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25</td>
<td>99.32 ± 0.12</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>GLC</td>
<td>100</td>
<td>101.17 ± 0.79</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50</td>
<td>100.90 ± 1.19</td>
<td>1.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25</td>
<td>100.92 ± 1.99</td>
<td>1.97</td>
</tr>
<tr>
<td></td>
<td>GLM</td>
<td>100</td>
<td>99.90 ± 0.11</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50</td>
<td>100.78 ± 0.21</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25</td>
<td>98.32 ± 0.41</td>
<td>0.42</td>
</tr>
</tbody>
</table>

**Selectivity and Specificity**
Selectivity of the method was checked by injecting the mixture solution into the column where three sharp peaks of metformin, gliclazide and glimepiride were obtained at retention times of 3.06, 4.33 and 6.00 minutes, respectively, and these peaks were not obtained for the blank solution.

Also, the specificity studies revealed that the presence of the excipients in the tablet formulations didn’t show any kind of impurity interference with the sharp and well-resolved peaks of metformin, gliclazide and glimepiride (Fig. 3B).

**Robustness**
The robustness of the methods was evaluated by making deliberate subtle changes (± 0.05) in the flow rate, pH of mobile phase and mobile phase composition ratio keeping the other chromatographic conditions constant. The changes effect was studied on the basis of percent recovery and standard deviation of all drugs. Table 5 shows that the changes had negligible influences on the results as revealed by small SD values.

**Limits of detection and limits of quantification**
For determining the limits of detection and quantitation, the method based on signal-to-noise ratio (3:1 for LOD & 10:1 for LOQ) was adopted. Limits of detection were reported to be 0.05, 1.21 and 0.11 µg/mL, while limits of quantification were calculated to be 0.17, 4.05 and 0.39 µg/mL for metformin, gliclazide and glimepiride, respectively (Table 2). These results show that the proposed method is highly sensitive and applicable for pharmaceutical studies even if detection of small concentrations is required.

**Analysis of tablet formulations**
Glucophage®, Gliclazide® and Glaryl® tablets containing metformin, gliclazide and glimepiride had been successfully analyzed by the proposed method. Excipients and impurities did not show interference indicating high specificity of the method. Results obtained were compared to those obtained by applying reference methods [6, 24] where Student’s t-test and F-test were performed for comparison. Results shown in Table 6 indicated that calculated t and F values were less than tabulated ones for metformin, gliclazide and glimepiride which in turn indicate that there is no significant difference between proposed method and reference ones relative to precision and accuracy.
TABLE 5. Results of the robustness for the determination of 50 µg/mL metformin (MET), glibizide (GLC) and glimepiride (GLM) using the proposed method.

<table>
<thead>
<tr>
<th></th>
<th>MET</th>
<th></th>
<th>GLC</th>
<th></th>
<th>GLM</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean recovery ± SD</td>
<td>CV (%)</td>
<td>Accuracy %</td>
<td>Mean recovery ± SD</td>
<td>CV (%)</td>
<td>Accuracy %</td>
</tr>
<tr>
<td>Flow rate 0.95 mL (-0.05)</td>
<td>99.63 ± 1.38</td>
<td>1.91</td>
<td>-0.37</td>
<td>101.85 ± 1.67</td>
<td>2.80</td>
<td>1.86</td>
</tr>
<tr>
<td></td>
<td>100.60 ± 1.74</td>
<td>3.05</td>
<td>0.56</td>
<td>100.50 ± 1.69</td>
<td>2.85</td>
<td>0.48</td>
</tr>
<tr>
<td>Flow rate 1.05 mL (+0.05)</td>
<td>99.48 ± 1.11</td>
<td>1.24</td>
<td>-0.51</td>
<td>100.95 ± 0.85</td>
<td>0.72</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>100.50 ± 1.69</td>
<td>2.85</td>
<td>0.48</td>
<td>100.40 ± 1.64</td>
<td>2.71</td>
<td>0.39</td>
</tr>
<tr>
<td>Buffer pH 3.15 (-0.05)</td>
<td>99.44 ± 1.03</td>
<td>1.06</td>
<td>-0.56</td>
<td>101.29 ± 0.74</td>
<td>0.54</td>
<td>1.29</td>
</tr>
<tr>
<td></td>
<td>100.30 ± 1.63</td>
<td>2.65</td>
<td>0.30</td>
<td>100.40 ± 1.64</td>
<td>2.71</td>
<td>0.39</td>
</tr>
<tr>
<td>Buffer pH 3.25 (+0.05)</td>
<td>99.44 ± 1.04</td>
<td>1.08</td>
<td>-0.55</td>
<td>101.51 ± 1.03</td>
<td>1.06</td>
<td>1.52</td>
</tr>
<tr>
<td></td>
<td>100.40 ± 1.64</td>
<td>2.68</td>
<td>0.40</td>
<td>100.40 ± 1.65</td>
<td>2.74</td>
<td>0.42</td>
</tr>
<tr>
<td>MeOH : Buffer 70.50:29.50</td>
<td>99.80 ± 1.72</td>
<td>2.97</td>
<td>-0.20</td>
<td>100.49 ± 1.65</td>
<td>2.75</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>100.40 ± 1.65</td>
<td>2.74</td>
<td>0.42</td>
<td>100.40 ± 1.64</td>
<td>2.71</td>
<td>0.39</td>
</tr>
<tr>
<td>MeOH : Buffer 69.50:30.50</td>
<td>99.47 ± 1.08</td>
<td>1.17</td>
<td>-0.53</td>
<td>100.72 ± 1.21</td>
<td>1.48</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>100.40 ± 1.64</td>
<td>2.71</td>
<td>0.39</td>
<td>100.40 ± 1.64</td>
<td>2.71</td>
<td>0.39</td>
</tr>
</tbody>
</table>
Conclusion

The presented method was developed and validated for rapid simultaneous estimation of metformin, gliclazide and glimepiride within 6 minutes. The results obtained indicate that the proposed method is rapid, accurate, sensitive, selective, robust and reproducible. This analytical method can be also adequate and useful for the pharmaceutical and quality control studies regarding metformin, gliclazide and glimepiride tablet combinations according to ICH guidelines.

Acknowledgments

The authors would like to thank the Bioequivalence and Accurate Measurement Unit, Zagazig University for facilitating and conducting the spectroscopic and chromatographic study.

Compliance with Ethical Standards

Conflict of interest

The authors declare that there is no conflict of interest in the manuscript.

Ethical approval

This manuscript does not include any studies on human or animals.

References


<table>
<thead>
<tr>
<th>TABLE 6. Statistical analysis of results obtained by the proposed HPLC method applied on Glucophage®, Gliclazide® and Glaryl® tablets compared with reference methods.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET (Glucophage®)</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Mean Recovery</td>
</tr>
<tr>
<td>SE</td>
</tr>
<tr>
<td>Variance</td>
</tr>
<tr>
<td>Student-t</td>
</tr>
<tr>
<td>F-test</td>
</tr>
</tbody>
</table>

* and # are the Theoretical Student t-values and F-ratios at p=0.05.
http://dx.doi.org/10.1155/2013/726235


 طريقه سريعه لفصل وتحديد ثلاثه مركبات من الأدويه الخافضه لسكر الدم وهم ميتفورمين، جليكلازيد وجليمبيرايد في وقت واحد باستخدام كروماتوجرافيا السوائل ذات الكفاءة العالية في صوره الاقراص

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يصف هذا البحث طريقه جديده و سريعه لفصل وتحديد ثلاثه مركبات من الأدويه الخافضه لسكر الدم وهم ميتفورمين، جليكلازيد وجليمبيرايد في وقت واحد باستخدام كروماتوجرافيا السوائل ذات الكفاءة العالية في صوره الاقراص.


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