Pharmaceutical Evaluation of Metformin HCl Products Available in the Jordanian Market

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ABSTRACT

Five brands of metformin HCl tablets that are commercially available in the Jordanian market were subjected to analysis according to the British Pharmacopea (2007) monograph. The tested criteria of the preparations included identification, assay and dissolution performance. The obtained results indicated that all of the examined products were in accordance with the pharmacopeal specifications. However, dissolution profile comparisons, which are not required by British Pharmacopea, revealed potentially serious differences in the performance of the studied products. According to similarity factor calculations, only one generic product was found to have similar dissolution profile to the originator (similarity factor (74.3). The other products showed similarity factors less than 50. Therefore only one generic can be said to be exchangeable with the originator. Further investigation might be conducted to confirm such results.

Keywords: Metformin, Dissolution, Quality control, Pharmaceutical tablets.

INTRODUCTION

As the quality of medicines concerns both health officials and general public; frequently, questions are raised regarding the quality of pharmaceutical products in the market. Such questions may include the extent of availability of counterfeit medicines in the local market and to what extent generics were equivalent to the originator (proprietary) medicine. The problem of low quality medicines appears to be so severe¹⁻² that has led to a program known as Drug Quality and Information Program which aims at raising awareness of the problem and fighting it. According to the program it is estimated that 10-35% of medicines in Asia were either improperly made or illegally produced³.

According to the World Health Organization (WHO)⁴, counterfeit drugs are defined as those which are deliberately or intentionally and fraudulently mislabeled with respect to identity and /or source. Substandard drugs on the other hand are those produced by legitimate manufacturers but don’t meet pharmacopoeial standards.

The quality of pharmaceutical products might be judged by quantitative and qualitative pharmacopeal analysis. Ideally, analysis of pharmaceutical products starts during manufacturing and continues after registration and marketing. Perhaps only few countries have regulatory authorities that analyse pharmaceutical products before and after registration (5). This is obviously due to large economic and technical burden which would governments have to cope with in case of adopting such policies.

In Jordan there is a well established regulatory system together with reasonably equipped quality control laboratories to test the quality of the registered medicines. Recently, a new system of testing pharmaceutical products has been adopted by the Jordanian regulatory
agencies (Act No.48, year 2006). The system is based on random analysis of various batches of the registered pharmaceutical products rather than analyzing every single batch. Nevertheless, the question of interchangeability of generic drugs with the originator might still be a valid question in Jordanian market as it really has been in the industrialized countries. In effort to ensure interchangeability of generics with the originator, the regulatory authorities in Jordan required all generics to be supported with a suitable bioequivalence study before registration.

Previous studies have shown alarming serious levels of substandard medicines in some developing countries [6-8]. The most relevant of these was that reported by Kyriacos and co-workers (8) who studied the quality of amoxicillin formulations in some Arab countries including Jordan. The study concluded that 56% of the tested capsules did not meet the United States Pharmacopoeia (USP) requirements. Moreover, the study demonstrated that Jordanian market had the highest percentage of substandard amoxicillin samples (according to USP specifications). Therefore this study was performed to further investigate the quality of some other medicinal products in the Jordanian market, namely, metformin HCl (MF-HCL) tablets. Four generic brands of MF-HCL (Metforal®, Glymet®, Diaphage®, Formit®) tablets together with the originator (Glucophage®) were tested according to British Pharmacopoeia monograph (9). In addition, the dissolution profiles of the products were evaluated by similarity factor calculations. The results obtained were compared for various commercial preparations with respect to the originator (Glucophage®).

**Experimental**

**Chemicals and instruments**

All UV spectroscopic measurements were made using a Cary UV spectrophotometer. The performance of the instrument was qualified (performance qualification) according to potassium dichromate procedure described by BP 2007 (9). Adjustment of pH values were made using a Metler Toledo pH meter that was previously calibrated appropriately. Identification was carried out using a Shimadzo FTIR (Japan). The examined tablets were purchased from the local market in just the same way that the patient might have bought them from the pharmacy. A list of the tested products is shown in Table 1.

<table>
<thead>
<tr>
<th>Brand name*</th>
<th>Manufacturer</th>
<th>Batch No.</th>
<th>Manufacturing date</th>
<th>Expiry date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucophage®</td>
<td>Merck sante (France)</td>
<td>104326</td>
<td>10-2006</td>
<td>10-2011</td>
</tr>
<tr>
<td>Glymet®</td>
<td>Pharma International (Jordan)</td>
<td>182</td>
<td>1-2008</td>
<td>1-2010</td>
</tr>
<tr>
<td>Metforal®</td>
<td>Menarini International (Italy)</td>
<td>61555</td>
<td>3-2006</td>
<td>3-2011</td>
</tr>
<tr>
<td>Diaphage®</td>
<td>United Pharmaceuticals (Jordan)</td>
<td>3786</td>
<td>7-2007</td>
<td>7-2010</td>
</tr>
<tr>
<td>Formit®</td>
<td>DAD Pharmaceuticals (Jordan)</td>
<td>719</td>
<td>8-2007</td>
<td>8-2009</td>
</tr>
</tbody>
</table>

* All tablets were labeled to contain 500 mg of metformin HCl with the exception of Formit® which was labeled to contain 1000 mg.
In general the BP 2007 (9) procedures were employed for assay, identification and dissolution testing of the various products. However the procedures are described here in brief: for identification a quantity of the powdered tablets, containing 20 mg of MF-HCl, was mixed with 20 ml of absolute ethanol, filtered, evaporated to dryness and the residue was dried at 105 °C for 1 hr. IR spectra were recorded for the obtained residue using KBr method. For assay procedure; a quantity of the powdered tablets equivalent to about 0.1 g of MF-HCL was shaken with 70 ml of water for 15 minutes, diluted to 100 ml with water and filtered (solution A). 10 ml of the filtrate were diluted to 100 ml with water (solution B). 10 ml of solution B were further diluted to 100 ml of water (solution C). The absorbance of solution C was measured at the maximum at 232 nm and 798 was taken as the value of $A(1\%, 1\text{ cm})$.

For dissolution, the medium was 900 ml of 0.68% w/v of potassium dihydrogen orthophosphate adjusted to pH 6.8 by the addition of 1M sodium hydroxide. Type II dissolution apparatus was employed and the basket was rotated at 100 revolutions per minute. Samples were withdrawn, filtered, diluted as appropriate and measured at 233 nm taking 806 as the $A1\%, \text{ cm}$. While the pharmacopoeia specifies sampling at a single time point of 45 minutes, samples were taken at 0, 10, 20, 30, 40, 50 and 60 minutes. Thus dissolution profiles were obtained in addition to the standard test required by BP 2007 (9).

RESULTS AND DISCUSSION

A sample of the obtained FTIR spectra is shown in Fig. 1. Generally; the obtained spectra have matched each other and that of the reference MF-HCL spectrum provided by the BP 2007. The estimated percentage per labels, from the assay, together with their relevant statistical analysis, are shown in Table 2. The BP 2007 specifies a range of 95-105% of the stated amount of MF-HCL tablets. Accordingly all of the tested tablets are clearly in accord with the BP specifications with the exception of Metforal® (91.87%). However, when the 95% confidence limit is considered (3.34) then the true percentage assay of Metforal® could be estimated as 95.2% which lies (marginally) within the BP 2007 specifications. Therefore it could be concluded, with 95% confidence, that all of the tested MF-HCL tablets satisfied the BP 2007 specifications.

<table>
<thead>
<tr>
<th>Product</th>
<th>Assay %</th>
<th>Standard deviation</th>
<th>95% confidence limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucophage®</td>
<td>98.25</td>
<td>0.94</td>
<td>1.51</td>
</tr>
<tr>
<td>Glymet®</td>
<td>98.06</td>
<td>1.63</td>
<td>2.62</td>
</tr>
<tr>
<td>Diaphage®</td>
<td>100.75</td>
<td>0.81</td>
<td>1.29</td>
</tr>
<tr>
<td>Metforal®</td>
<td>91.87</td>
<td>2.11</td>
<td>3.34</td>
</tr>
<tr>
<td>Formit®</td>
<td>100.42</td>
<td>2.91</td>
<td>4.61</td>
</tr>
</tbody>
</table>
The dissolution test according to BP 2007 requires that not less than 70% of the active ingredient should dissolve within 45 minutes \(^9\). All the tested products have satisfied this requirement and thus were in accord with the BP 2007 specifications (Fig. 2). However, in this study a complete dissolution profile was obtained for each product Fig. 2. It is obvious from Fig. 2 that various products exhibit different dissolution profiles. In order to judge whether these differences in dissolution profiles were significant, all dissolution profiles were compared to that of the originator (Glucophage®) using the similarity factor \(f_2\) value recommended by FDA \(^{10}\). The obtained values of \(f_2\) were: 24.5, 74.3, 39.4 and 28.2 for Metforal®, Glymet®, Diaphage® and Formit®, respectively. Thus, only Glymet® exhibited \(f_2\) value higher than 50. Accordingly, the three generic preparations: Metforal®, Diaphage® and Formit® were found nonequivalent in their dissolution profile to the originator (Glucophage®). Only Glymet® seems to be equivalent in its dissolution profile to the originator. However, it is uncertain if these differences in dissolution profiles of the different preparations might be reflected in their invivo pharmacological effect. Previous studies have demonstrated correlation between dissolution pattern of MF-HCL tablets (immediate and controlled release) and their bioavailability \(^{11-12}\). Therefore it is
very likely that the observed differences between dissolution profiles of the tested generics and the originator reflect real differences in their bioavailability. Consequently, Metforal®, Formit® and Diaphage® might not be interchangeable with the originator. These findings don’t necessarily indicate a shortcoming on the side of the control laboratories at the regulatory authority but rather an insuitability of the BP 2007 dissolution requirements for detecting differences in performance of the various commercial MF-HCL tablets. On the other hand, all generics must have shown bioequivalence to the originator if they were to be registered in Jordan. But if they were bioequivalent then they should essentially exhibit similar dissolution profiles. Therefore, it could be seen that there are some gaps in the regulatory system, which allowed the presence of such apparently not equivalent generics in the Jordanian market. One potential explanation of such gaps might be the inconsistency of the manufactured lots of pharmaceutical tablets so that the one used for bioequivalence study was really equivalent to the originator, while other produced batches might be of different quality. Even if that was the scenario, it also indicates presence of gaps in the regulatory system that need to be overcome.

**Fig. 2:** Dissolution profiles of the different brands of MF-HCL tablets. Each data point is the average of 6 determinations. In all cases the estimated error was less than +/- 5%.

Overall, it can be recommended that activation of the present regulations is required regarding the control of pharmaceutical products. Perhaps new regulations might also be necessary particularly concerning post marketing evaluation of the marketed products.

**CONCLUSION**

Four generic brands of MF-HCL tablets (Metforal®, Diaphage®, Glymet®, Formit®) together with the originator (Glucophage®) have been subjected to analysis according to the monograph of British Pharmacopoeia (9). The results have shown that all the tested brands satisfied the BP (9),
requirements in terms of identification, assay and dissolution. As such these results negate the frequent thoughts that some medicines on the Jordanian market might not be of the required standards. On the other hand, extra-pharmacopeal tests (dissolution profiles) revealed potentially significant differences between the different generics and the originator. Only one generic product could be said to be equivalent to the originator while the other three were not. These findings support the need for activation of the regulatory rules with emphasis on post-marketing evaluation of pharmaceutical products.

REFERENCES

(5) USAID 2007. Ensuring the quality of medicines in resource-limited countries: an operational guide, united states pharmacopeia drug quality and information program, united states agency for international development.

The title of the article is not clearly visible due to the image quality. However, the text appears to be discussing a study involving artemisinin and its evaluation in the context of traditional Jordanian use.

The abstract mentions the research conducted by the Medical Faculty of the Jordan University of Science and Technology. The study examines the efficiency and safety of an injectable medicinal product containing artemisinin in the traditional market in Jordan. The study compares the injectable product with the British official product and finds that the local product has an efficiency of 74.3% with a 59% similarity when compared with the British product. The results indicate that the traditional market injectable product can be used without inconvenience.

Keywords: Medicinal Product, Efficiency, Safety,比較, Traditional Market, Efficiency.