Pharmaceutical Evaluation of Metformin HCl Products Available in the Jordanian Market

***Imad Ibrahim Hamdan*[1]✉, *Ahmed Khalid Bani Jaber*[1]**

[1] Department of Pharmaceutical Sciences, University of Jordan, Amman, Jordan.

ABSTRACT

Five brands of metformin HCl tablets that are commercially available in the Jordanian market were subjected to analysis according to the British Pharmacopoea (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 Pharmacopoea, 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 severe[1-2] 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 produced[3].

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 pharmacopoeal 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

Received on 25/2/2009 and Accepted for Publication on 16/4/2009.

✉ E-mail: iimad68@yahoo.com

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 Pharmacopea 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.

Table1: A list of the tested commercial tablets of metformin HCl available in the Jordanian market.

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

* 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 ^{o}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 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%, 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. Thus the substance present in each of the tested tablets was positively identified as MF-HCl. 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 2: Summary of assay results of the tested tablets together with statistical analysis (n =4). BP 2007 specification states that the percentage assay = 95-105%.

Product	Assay %	Standard deviation	95% confidence limit
Glucophage®	98.25	0.94	1.51
Glymet®	98.06	1.63	2.62
Diaphage®	100.75	0.81	1.29
Metforal®	91.87	2.11	3.34
Formit®	100.42	2.91	4.61

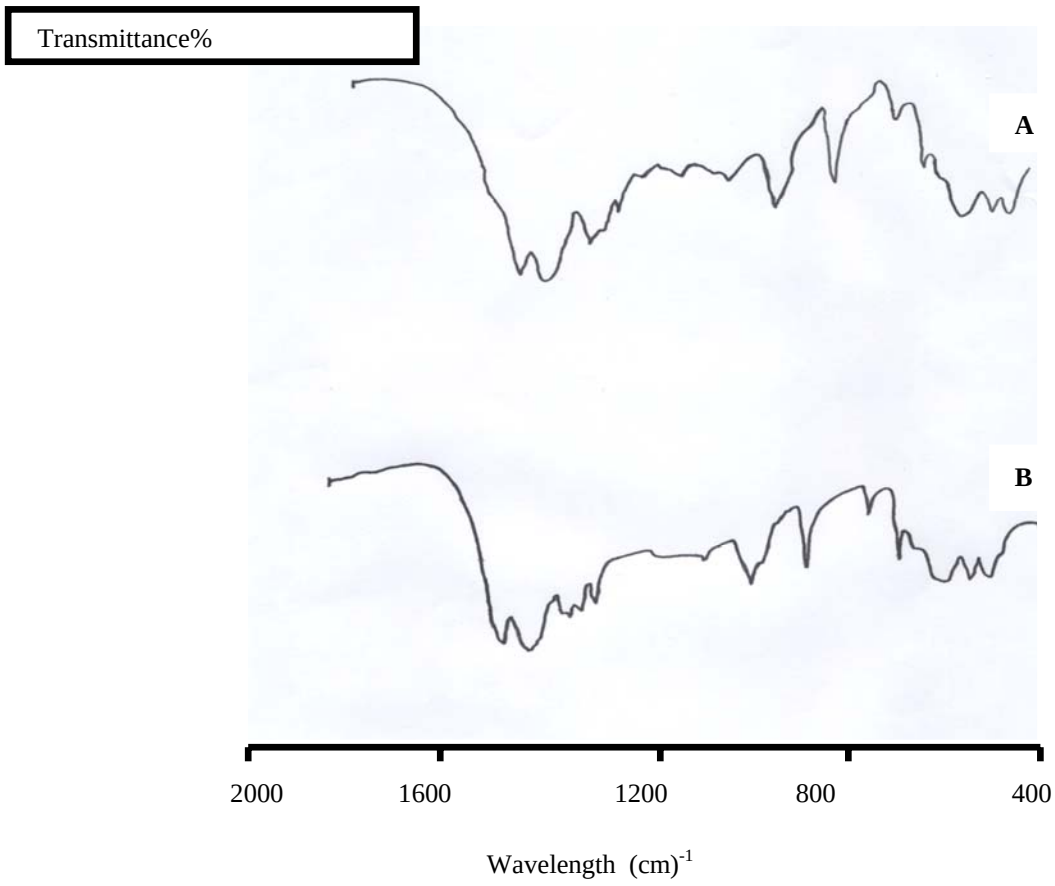

Fig. 1: Selected FTIR spectra for extracted substance from Glucophage® (A) and the reference spectrum of MF-HCl provided by the British Pharmacopoeia (B).

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 bathes 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.

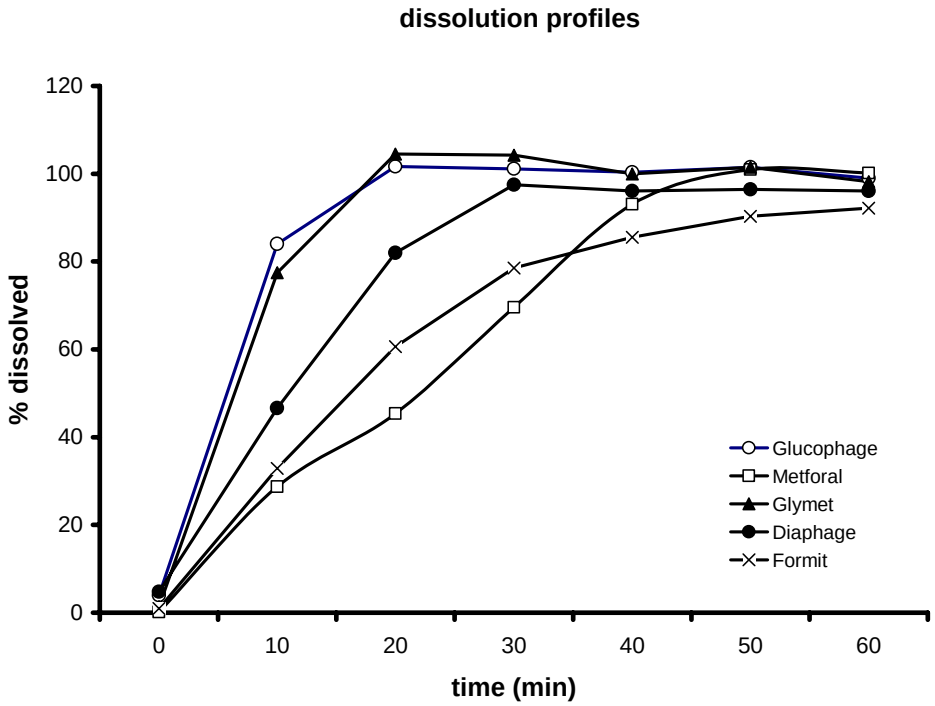

Fig. 2: Dissolution profiles of the different brands of MF-HCL tablets. Each data point is the average of 6 determinations. In all cases the estimated error was less than +/- 5%.

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

(1) Afu S. Incidence of substandard drugs in developing countries. *Trop. Med. Int. Health.* 1999; 4: 72-73.

(2) Caudron J.M., Ford N., Henkens M., Macé C., Kiddle-Monroe, R. and Pinel, J. Substandard medicines in resource-poor settings: a problem that can no longer be ignored.*Trop. Med. Int. Health.* 2008; 13:1062-1072.

(3) Drug Quality and Information Program 2004. http://www.uspdqi.org or http://www.usp.org/ worldwide/dqi.

(4) WHO 1999. Counterfeit drugs: guidelines for the development of measures to combat counterfeit drugs, Department of essential Drugs and other Medicines. Geneva: WHO.

(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.

(6) Shakoor O., Taylor R.B. and Behrens R.H. Assessment of the incidence of substandard drugs in developing countries. *Trop. Med. Int.Health.*1997; 2: 839-845.

(7) Taylor R.B., Shakoor O. and Behrens R.H. Pharmacopoeial quality of drugs supplied by Nigerian pharmacies. *Lancet* 2001; 357: 1933-1936.

(8) Kyriacos S., Mroueh M., Chahine R.P. and Khouzam O. Quality of amoxicillin formulations in some Arab countries.*J. Clin. Pharm. Ther.* 2008; 33: 375-379.

(9) BP 2007. British Pharmacopoea, Vol 2. Metformin HCl monograph, London, The stationary Office.

(10) Polli J.E., Rekhi S., Augsburger L.L. and Shah V.P. Methods to compare dissolution profiles and a rationale for wide dissolution specifications for metoprolol tatrtarate tablets. *J. Pharm. Sci.* 1997; 86: 690- 700.

(11) Balan G., Timmins P., Greene D.S. and Marathe P.H. In vitro-in vivo correlation (IVIVC) models for metformin after administration of modified-release (MR) oral dosage forms to healthy human volunteers. *J. Pharm. Sci.* 2001; 90:1176-1185.

(12) Pentikäinen P.J. Bioavailability of metformin. Comparison of solution, rapidly dissolving tablet, and three sustained release products. *Int. J. Clin. Pharmacol. Ther. Toxicol.* 1986; 24:213-220.

التقييم الصيدلاني لمستحضرات جنيسة من ميتفورمين هيدروكلورايد متوفرة في السوق الأردني

عماد حمدان[1]، أحمد بني جابر[1]

[1] قسم العلوم الصيدلانية، كلية الصيدلة، الجامعة الأردنية

ملخـص

تم فحص خمس مستحضرات جنيسة من الأقراص المحتوية على مادة ميتفورمين هيدروكلورايد متوفرة في السوق الأردني حسب ما ورد في دستور الأدوية البريطاني (2007). تضمنت الفحوص الكشف عن هوية المادة الفعالة ونسبة المحتوى بالقرص وكذلك معدل الإنحلال. تبين النتائج أن جميع المستحضرات التي تم فحصها تتطابق مع مواصفات دستور الأدوية البريطاني. كذلك تمت مقارنة منحنى الإنحلال لكل من الأدوية الجنيسة مع منحنى إنحلال الدواء الأصيل من خلال حساب عامل التشابه (وهذا غير مطلوب حسب دستور الأدوية البريطاني) وقد تبين أن هناك دواء جنيس واحد فقط يطابق في ذلك الدواء الأصيل (عامل التشابه = 74.3). أما الأدوية الجنيسة الأخرى فقد أظهرت عوامل تشابه أقل من 50. بالتالي يمكن القول وبناءا على هذه النتائج أن الدواء الأصيل يمكن ابداله بدواء جنيس واحد فقط. المزيد من الدراسات ربما يؤكد هذه النتائج.

الكلمـات الدالـة: ميتفورمين، المادة الفعالة، معدل الانحلال، ضبط الجودة، أقراص دوائية.

تاريخ استلام البحث 2009/2/25 وتاريخ قبوله للنشر 2009/4/16.