East and Central African Journal of Pharmaceutical Sciences
Vol. 24 (2021) 85-89

Short Communication

Quality of Metformin Tablet Products in the Kenyan Market

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The quality of 14 metformin hydrochloride tablet products locally available in the Kenyan market is reported. The samples composed both 500 mg and 850 mg strengths. The compendial tests performed included uniformity of weight, disintegration, friability, hardness, assay and dissolution. Assay and dissolution were determined by ultra-violet spectrophotometry. All the samples had a deviation of less than ± 5% from the mean average weight in the uniformity of weight test, disintegrated within 5-17 minutes and had a friability of less than 1%. They yielded satisfactory hardness and acceptable dissolution within 45 minutes. However, two samples failed to meet the British Pharmacopoeia specifications for assay.

Keywords: Metformin, drug quality, uniformity of weight, disintegration, friability, hardness, dissolution, assay.

INTRODUCTION

Quality of drugs is an important part of effective health care delivery. Presence of substandard and falsified medicines is a major concern globally, but it is particularly significant in developing countries due to weak legislation and inadequate post-market surveillance frameworks [1]. Surveillance of drugs circulating in the Kenyan market over the last four decades has shown that quality varies with the type of drug. Furthermore, quality problems were encountered with both locally manufactured and imported drugs. The classes of drugs whose quality control results were most commonly reported were antibacterials, analgesics, antimalarials, antiretrovirals, antifungals, antihypertensives and antiulcer agents [2-12].

Metformin hydrochloride is a biguanide oral hypoglycemic agent used as a first-line drug in the treatment of type 2 diabetes mellitus. It is widely used clinically owing to its advantages such as euglycaemic and weight reduction properties as well as its availability and affordability. Studies from various countries reveal presence of substandard metformin tablets in specific markets. A survey carried out in Ghana found that all 14 brands tested complied with compendial specifications on identity, weight uniformity, disintegration and hardness, whereas one brand failed in friability and three failed the assay test [13]. From a sample of eight brands evaluated in Nigeria, one brand failed the British Pharmacopoeia (BP) requirements for friability and only four met the assay and dissolution specifications [14]. Two out of four brands analyzed in India failed assay, but all samples passed the dissolution test [15]. Another study in Trinidad and Tobago found all four brands analyzed compliant in friability and disintegration tests while one brand failed in assay [16]. All five brands in a Syrian study complied with the uniformity of weight and friability test, with three brands failing the hardness test, and two each not complying with assay and dissolution [17]. On the contrary, all six brands studied in Saudi Arabia satisfied the United States Pharmacopoeia (USP) specifications for identification, assay and dissolution [18].

There has been no published data on the quality of oral hypoglycemic drugs in Kenya derived from post market surveillance. In one report on quality of different drugs over a five-year period,

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two imported brands of metformin complied with specifications [11]. Thus, the purpose of this study was to assess the quality of metformin products in Kenya.

MATERIALS AND METHODS

Samples

The total number of metformin-containing products registered by Pharmacy and Poisons Board (PPB) at the time of the study was 106 (18 local and 88 imported) inclusive of combination products [19]. The target population for this study was the 500 mg and 850 mg metformin only products of which the registered drugs were found to be 37 (8 local and 29 imported). Out of these products, 14 were readily available in the Kenyan market and this ended up being the sample size for this study. Samples were randomly obtained from community pharmacies in Nakuru and Nairobi to make a total of 14 samples each representing one batch. Nine brands consisting of two local and seven imported products were available in one strength while five brands existed in both 500 mg and 850 mg forms. The brands studied included Glucomet® (Cosmos, Kenya), Diaphage® (Universal Corporation Ltd, Kenya), Lipimet® (Prism Life Sciences Ltd, India), Metformin Denk® (Denk Pharma, Germany), Novartis Access® (Lek S.A., Poland), Metforal® (Menarini-Von Heyden, Germany), Glucophage® (Merck, France), Glyformin® (Remedica, Cyprus) and Comet® (Square Pharmaceuticals Ltd, Bangladesh).

Reagents and solvents

Analytical grade KH_2PO_4 and NaOH were from Loba Chemie PVT Ltd (Mumbai, India). Distilled water was freshly prepared in the Drug Analysis and Research Unit (DARU) laboratory, University of Nairobi.

Instrumentation

A Genesys ultraviolet (UV) spectrophotometer 10 S (Waltham, Massachusetts, USA) was used to determine the absorbances of the samples whereas a Schleuniger Pharmatron 2E (Thun, Switzerland) electronic tablet hardness tester was used to assess the tablet hardness. An Erweka tablet friability tester TA3R, Erweka disintegration machine ZT3 (Ahmedabad, India) and Electrolab dissolution tester (Mumbai, India) were used to determine friability, disintegration and dissolution of the tablets, respectively.

Methods

All tests were performed according to the BP specifications [20] except dissolution which followed the USP method [21].

Uniformity of weight: Twenty tablets of metformin hydrochloride tablets were selected randomly and each of them weighed separately. The mean weight and the deviation from the mean weight were computed.

Disintegration test: One tablet of metformin was placed in each of the six baskets of a disintegration apparatus containing distilled water maintained at 37±2 ℃. The time taken for each tablet to disintegrate was recorded.

Friability test: A total of 20 tablets were randomly sampled, dusted and accurately weighed prior to testing. The tablets were placed in a friabilator drum and rotated 100 times after which the tablets are dusted and weighed. The percentage friability was calculated.

Hardness test: Six metformin tablets were weighed individually and the diameter and tablet thickness determined. The tablets were subjected to the hardness tester, crushed and the crushing strength reading recorded. The tensile strength of the tablets was calculated.

Assay: A sample of 20 tablets was weighed and powdered. A quantity of powder containing 0.1 g of metformin hydrochloride was shaken with 70 ml of water for 15 min and diluted to 100 ml with water, filtered, discarding the first 20 ml of filtrate. Ten ml of the filtrate was diluted to 100 ml with water and 10 ml of the resulting solution further diluted to 100 ml. The absorbance of the resulting solution was measured at 232 nm. The content of metformin hydrochloride tablets was calculated taking $A_{1\,cm}^{1\%}$ as 798 according to BP specifications.

Dissolution test: The dissolution medium (900 ml) composed of 0.68% w/v KH_2PO_4 was pH

adjusted to 6.8 using NaOH solution. The baskets were set to rotate at 100 rpm. After 45 min, a 10 ml aliquot was withdrawn, filtered and the filtrate diluted to 100 ml with water. Ten ml of the resulting solution, was further diluted to 100 ml with water, filtered and the absorbance was determined at 232 nm. The metformin HCl content was calculated using 806 as the value of $A_{1\ cm}^{1\%}$.

RESULTS AND DISCUSSION

Table 1 shows the uniformity of weight, disintegration, friability, hardness, assay and dissolution values obtained for the 14 metformin tablet samples tested.

All the 14 samples complied with BP specifications for uniformity of weight, disintegration, friability and hardness [19]. With regard to the assay results, two imported samples (M500-2 and M500-5) did not comply with the BP specifications for assay (Table 1). The manufacturer of M500-2 was the same as that of M850-2, which complied in the assay test. The rest of the samples were compliant with assay values ranging 96.2-103.4% of the label claim.

Table 1: Results of mean weights, weight deviation, friability, hardness, disintegration, assay and dissolution for metformin HCl tablets

Drug code	Mean weight (mg)	Highest Weight Deviation (%)	Friability (%)	Hardness (N)	Highest disintegration time (min)	Assay (% label claim)	Average dissolution (%), (n=6)
M500-1	601.34	-2.68	0.82	70.0	8.33	96.2	98.9
M500-2	652.29	1.59	0.16	78.7	6.00	94.2*	99.3
M500-3	654.19	-1.66	0.08	91.7	13.29	101.5	95.2
M500-4	520.63	3.36	0.00	158.0	9.10	96.6	95.3
M500-5	561.76	2.46	0.09	116.7	9.20	92.1*	99.1
M500-6	534.22	4.57	0.00	124.8	10.29	97.4	97.5
M500-7	633.14	-4.22	0.15	113.5	6.55	100.7	98.4
M850-1	1034.93	3.55	0.10	178.2	9.02	100.1	98.7
M850-2	964.87	2.78	0.11	117.7	19.43	100.9	97.2
M850-3	1080.07	-4.97	0.23	124.3	8.51	103.4	98.2
M850-4	949.10	1.59	0.00	149.7	14.30	98.9	99.1
M850-5	1036.45	1.54	0.10	200.0	7.21	103.1	99.4
M850-6	879.29	3.38	0.00	109.7	13.52	100.7	87.2
M850-7	945.51	2.00	0.16	99.5	16.12	97.0	95.6

*Sample does not comply with the BP specifications.

Dissolution test: Table 1 shows the average percentage dissolved after 45 min for each brand. The USP states that "not less than 70% (Q) of the labeled amount should be dissolved in 45 min". The lowest average percent dissolved was 87.2%. The rest of the samples had 95.2-99.4% of drug dissolving within 45 min. The acceptance criteria for immediate release tablets states that "each unit should have a dissolution of not less than Q+5%", which in this case translates to 75% of the label claim. The tablet with the lowest individual dissolution recorded was 77.6% (results not shown). Therefore, all the samples tested complied with the USP (2019) specifications for dissolution of metformin hydrochloride tablets.

In this study, substandard metformin tablet brands were identified. Two samples of imported products failed in the assay specifications. Assay non-compliance has been a predominant problem with metformin tablets in other countries [13-17]. It is therefore important for manufacturers to adhere to current good manufacturing practices (cGMP) and drug regulatory authorities to improve pharmacovigilance as well as post market surveillance.

CONCLUSION

All the samples tested passed the uniformity of weight, disintegration, friability, hardness and dissolution tests while two samples failed the assay test. This study therefore underscores the need for continuous post-market surveillance of metformin products in order to avoid treatment failure in diabetic patients. Furthermore, the findings call for investigation of other classes of oral hypoglycaemic agents in Kenya.

ACKNOWLEDGEMENTS

The authors would like to thank Mr. J. Nguyo and Ms. J. Syombua of the Department of Pharmaceutical Chemistry, and Ms. A. Mathenge and Mr. R. Achoki of Department of Pharmaceutics and Pharmacy Practice, University of Nairobi, for technical support.

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