Comparative Evaluation of Metformin Hydrochloride Brands Available in Sri Lanka

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Abstract - Metformin, being noteworthy, is used in the management of Type 2 Diabetes. It is available in different brands in Sri Lanka. Several studies have shown that different brands of the drug varied qualities, which could impact the treatment efficacy. This study was conducted to analyse the quantity of different brands of metformin hydrochloride tablets available in the Jaffna municipal area, Sri Lanka. It was a laboratory-based exploratory study conducted in State Pharmaceutical Manufacturing Corporation, Sri Lanka. Based on most available brands at pharmacies in the Jaffna Municipal area, fifteen brands of conventional metformin tablets were selected for this study. They were coded as M_1, M_2, M_3,... M_{15}. The uniformity of weight, hardness, friability, disintegration, uniformity of content, and dissolution tests were performed in accordance with the British Pharmacopeia (BP). Two out of fifteen brands were locally manufactured, and the remaining were imported. All brands were conformed to BP specifications in uniformity of weight. The hardness test showed optimum withstanding strength in all brands. All brands excluding M_1 (108.95%), M_6 (111.58%), M_7 (94.27%) and M_{11} (93.91%) were comprised of values falling under monograph specifications (95% -105%) for uniformity of content. Twelve brands satisfied Pharmacopeia requirements in the friability test, while two brands, M_7 (40.45 min) and M_{10} (34.5 minutes), failed in the disintegration test. The dissolution of one brand showed the least drug release (61.40%), and the remaining passed the dissolution test. In conclusion, of all the metformin hydrochloride brands, nine brands passed all the official tests according to BP specifications.

Keywords: metformin, brands, evaluation, quality analysis

I. INTRODUCTION

Diabetes mellitus is a chronic, non-communicable metabolic disease distinguished by increased blood glucose levels. It is categorized as Type 1 and Type 2 Diabetes (WHO, 2006). Metformin, an oral hypoglycaemic drug belonging to the biguanides group, serves as the first-line treatment in managing Type 2 diabetes (International Diabetes Federation, 2005). Maintaining a steady-state plasma concentration of the drug is vital in drug therapy and is enhanced by the amount of drug available in metformin tablets in accordance with the amount prescribed. Different brands of the similar drug may express discrepancy from the prescribed amount, and it might alter the plasma steady state when a patient switch from one brand to another (Sougi et al., 2016).

Generally, the drugs are given with two different names: Generic name or Non-proprietary name and Brand name or Proprietary name (Thakkar and Billa, 2013). The generic name is the name of the active ingredient in the medicine decided by an expert committee and internationally understood and accepted. It is well-known that generic drugs are usually intended to be interchangeable with an innovator product which is formulated and marketed after the termination of the patent (WHO, 2013a). The most crucial aspect of generic drug development is the concepts of bioavailability and bioequivalence (Howland, 2009). The essential criterion utilized in confirming the interchangeability of a generic drug to the corresponding brand-name drug. The drug approval will be given when the generic drug meets the exact amount and type of active ingredient, route of administration, and therapeutic effectiveness as the original drug (Borgheini, 2003).

The drugs of the self-same group are considered to be chemically and bio pharmaceutically equivalent to each other when they are alike in quality, strength,

purity, and active ingredient release profile (Adegbolagun et al., 2007). Quality control parameters are remarkable kits for maintaining the quality of different brands of Metformin (Awofisayo et al., 2010). Test for uniformity of weight ensures the consistency of dosage form while hardness test determines the physical strength of the tablet. Friability is the propensity of tablets to break into fragments, influencing product appearance and consumer acceptance. Apart from that, a disintegration test is essential in identifying the time taken for complete disintegration of tablets or capsules (Hettiarachchi et al., 2015). The dissolution test, as a surrogate marker for bioequivalence, plays a crucial role in monitoring the consistency of drug release among batches (Awofisayo et al., 2010).

Counterfeiting with inappropriate or insufficient ingredients, absence of active ingredients, or fake packaging is common in generic and branded products (WHO, 1999). Furthermore, substandard drugs are the products that are encountered with low specified qualities at laboratory testing (Taylor et al., 2001). Consumption of these under-quality medicines may result in treatment failure and lead to detrimental consequences (Petralanda, 1995). Metformin is one of the fast-moving oral hypoglycaemic drugs, with a wide range of different brands prescribed, especially for diabetes and other indications. This study aims to assess the quality control parameters of different brands of metformin hydrochloride conventional tablets available in the Jaffna municipal area, Sri Lanka, and compare them with the reference brand.

II. METHODOLOGY

This laboratory-based analytical study was carried out in the State Pharmaceutical Manufacturing Corporation (SPMC), Sri Lanka. Fifteen different brands of metformin hydrochloride tablets with a strength of 500 mg were selected for this study. A mini-survey was used to select brands. Metformin brands were selected based on mostly available brands in all registered pharmacies in the Jaffna municipal area. A total of 15 brands, including reference brands, were used in the study. The tablets with near expiry dates (within two months) were excluded. The samples were coded as M1, M2, M3, M4, M5, M6, M7, M8, M9, M10, M11, M12, M13, M14, and M15. Brand M2 was used as a reference brand.

A. Uniformity of weight

Twenty tablets were randomly selected from each brand and weighed collectively and individually. The average weight of each tablet and percentage deviation was determined for each brand (British Pharmacopoeia, 2017).

B. Hardness test

Ten tablets of each brand were randomly taken and placed between the spindles of the Pharma Test (Germany) hardness tester. It was diametrically compressed until fractured. The crushing strength of tablets from each brand was read and recorded

C. Friability test

The samples, each containing ten tablets from each brand, were used for this test. Tablets were dedusted and weighed together, and placed in the friabilator (Pharma test, 920, Germany). It was operated at 25 revolutions per minute for 4 minutes. The tablets were again dedusted and weighed. The percentage weight loss was calculated (British Pharmacopoeia, 2017). This test was done in triplicate for each brand.

D. Disintegration test

Three sets of samples, each containing six tablets, were used from each brand, and the disintegration time was determined at 37^{o}C using distilled water in the disintegration apparatus (Toyama Sangyo, NT4H5, Japan). The disintegration time of tablets was recorded (British Pharmacopoeia, 2017). Test was done in triplicate for all brands.

E. Dissolution test

USP 2 (basket type) digital tablet dissolution test apparatus (Pharma Test Apparatus, Germany) is operated at 100 revolutions per minute(rpm) using 900 mL of pH 6.8 Potassium dihydrogen orthophosphate buffer at 37 ± 0.50^{o} C. Six metformin tablets were taken, and one tablet was placed in each basket. The apparatus was operated at the interval of 10, 30 and 45 minutes. 10 mL of the sample was withdrawn at the interval of 10, 30, and 45 minutes and 10 mL of fresh dissolution medium was immediately added. The withdrawn sample was filtered by 0.45 µm syringe filter and diluted to 100 mL with distilled water. Again, 10 mL of the resultant diluted solution was diluted up to 100 mL with distilled water. The drug content of each sample was analyzed using UV – visible spectrometer, and the absorbance values were taken at a maximum wavelength of 233 nm (British Pharmacopoeia, 2017).

F. Uniformity of content test

Twenty tablets from each brand were used for this test. Tablets were crushed to powder. The tablet powder equivalent to 0.1 g of metformin hydrochloride was accurately weighed and added into 70 mL of distilled water. Then it was shaken for 15 minutes and made up to 100 mL with distilled water. It was filtered through Whatman filter paper (no 5), and initial 20 mL was discarded. 10 mL of the filtrate was taken and diluted to 100 mL with distilled water. 10 mL of the resulting solution was diluted again to 100 mL with distilled water. The absorbance of the final solution was determined at a wavelength of 232 nm using a UV spectrometer (British Pharmacopoeia, 2017). This test was done in triplicate for each brand.

All test readings were presented as mean with standard deviation. The data were computed and analyzed by using SPSS 21 (Statistical Package of Social Science). One-way ANOVA was used to determine the significant difference between the brands and reference. 95% confidence interval was used in this study, and a p-value less than 0.05 was considered a statistically significant difference.

III. DISCUSSION AND ANALYSIS

The metformin tablets included in the study were used before their expiry dates. Among the selected brands, eleven brands were from India (M1, M3, M5, M6, M7, M8, M9, M10, M11, M13, and M14) and one brand from Pakistan(M2), and one brand from Bangladesh (M4) while two brands were manufactured locally in Sri Lanka (M12 and M15). Tables 1 and 2 show the quality parameters of different parameters of metformin brands. All tests were done in triplicate, and the results of all tests were presented as mean with the standard deviation.

The weight uniformity test revealed that all the brands were conformed to British Pharmacopoeia, as the percentage weight deviation of tablets was not greater than 5% for all brands. In order to pass the uniformity of weight, not more than two of the individual weight of the tablets can deviate from the average weight by more than a percentage deviation of ±5%, and none should deviate by more than 10% (British Pharmacopoeia, 2017). Similar studies in Sri Lanka (Hettiarachchi et al., 2015), Syria (Mansour and Isbera, 2016), and West Indies (Gupta and Gupta, 2016) also showed that all brands of Metformin were within BP limit. However, another study in Sri Jayewardenepura, Sri Lanka, reported that one batch out of fifteen batches from five brands failed to comply with the uniformity of the weight test (Nelumdeniya et al., 2012).

Table 1. Quality evaluation parameters of Metformin tablets

Code	Uniformity of Weight (g)	Hardness (Kgf)	Friability (%)
M_1	0.5605 ± 0.016	9.7 ± 0.636*	0.0214 ± 0.0004
M_2 Ref	0.5246 ± 0.006	15.74 ± 0.838	0.0172 ± 0.0002
M_3	0.6063 ± 0.019	10.36 ± 0.835*	0.0435 ± 0.0006*
M_4	0.6223 ± 0.008	8.26 ± 0.802*	0.0433 ± 0.0012*
M_5	0.5664 ± 0.014	12.46 ± 1.999*	0.0248 ± 0.0008
M_6	0.5763 ± 0.011	12.36 ± 0.635*	1.1111 ± 0.1540*
M_7	0.5595 ± 0.015	17.24 ± 0.684	0.0214 ± 0.0014
M_8	0.5643 ± 0.006	8.82 ± 1.112*	1.2888 ± 0.1890*
M_9	0.5463 ± 0.010	7.94 ± 0.152*	1.2288 ± 0.0230*
M_{10}	0.5826 ± 0.012	9.82 ± 0.277*	0.0274 ± 0.0015
M_{11}	0.7004 ± 0.007	18.26 ± 1.119*	0.0057 ± 0.0011
M_{12}	0.6254 ± 0.004	17.26 ± 1.547	0.0064 ± 0.0006
M_{13}	0.6439 ± 0.009	12.28 ± 1.381*	0.0197 ± 0.00023
M_{14}	0.5834 ± 0.011	22.4 ± 0.656*	0.0103 ± 0.0005
M_{15}	0.6065 ± 0.009	13.32 ± 1.794*	0.0049 ± 0.0007

*Statistical significance ($p < 0.05$)

Brands manufactured from India showed both the highest hardness (M14, 22.4 Kgf) and the lowest hardness (M9, 7.94 Kgf). The crushing force of 6 ± 2 Kgf was considered as the minimum force for a quality tablet (Uddin et al., 2017). Statistical significance was observed between all brands excluding M7 and M12 to reference brand, M2 at $p < 0.05$. According to the Pharmacopoeial limit, tablets should not have a friability value larger than 1.0% w/w (British Pharmacopoeia, 2017). Out of all brands, M6, M8, and M9 failed the friability test. Statistically, a difference was observed among M3, M4, M6, M8, and M9 with reference brand M2 ($p < 0.05$). The failure of these three brands could be due to the use of an insufficient binder or inappropriate compaction force, making the tablets friable (Afifi et al., 2013).

Table 2. Disintegration and dissolution profile of Metformin tablets

Code	Disintegration Time(min)	Drug release (%) in 45 minutes
M_1	9.65 ± 0.778	94.53 ± 2.31
M_2 Ref	12.1 ± 0.990	92.29±0.57
M_3	11.3 ± 1.697	99.82±1.75*
M_4	2.50 ± 0.566*	97.97±2.64
M_5	8.55 ± 2.192	96.49±1.76
M_6	16.45 ± 0.212*	95.45±3.16
M_7	40.45 ± 1.909*	61.40±0.99*
M_8	9.2 ± 1.273	88.45±1.56
M_9	19.15 ± 1.061*	86.32±8.99
M_{10}	34.5 ± 0.849*	87.36±1.32
M_{11}	3.575 ± 0.530*	92.14±1.76
M_{12}	12.3 ± 0.707	99.63±2.24*
M_{13}	9.5 ± 0.849	92.41±2.56
M_{14}	10.1 ± 0.849	91.65±1.91
M_{15}	9.55 ± 1.202	101.02±1.37*

*Statistical significance ($p< 0.05$)

The disintegration time measures the time required for a tablet to disintegrate into particles when in contact with the gastrointestinal fluid (Giri et al., 2012). According to this study, the maximum disintegration time was 40.45 minutes for a brand from India (M7), and the minimum was 2.5 minutes for a brand from Bangladesh (M4). British Pharmacopoeia (2017) stipulated that the disintegration time should be within 15 minutes for an uncoated tablet and 30 minutes for film-coated tablets. The tablets tested in this study were film-coated, and it is clear that M7 (40.45 min) and M10 (34.5 minutes) failed to achieve the standard. Although M11 and M14 had considerably higher values for hardness than the innovator brand (M2), they showed a significantly low disintegration time. This could be due to different disintegrants employed to improve the penetration of aqueous liquids (Afifi et al., 2013)). Identical studies were manifested with all brands passing the disintegration test in accordance with BP (Nelumdeniya et al., 2012; Hettiarachchi et al., 2015).

The British Pharmacopoeia (2017) specifies that the content of active pharmaceutical ingredients should not be less than 95% and not more than 105%. All brands except M1 (108.95%), M6 (111.58%), M7 (94.27%), and M11 (93.91%) comprised values within the monograph specifications. A Study in India reported that all four brands of Metformin were within the BP limitation (Sachan, Kumar, and Gupta, 2016). A dosage form having a higher percentage of drugs than it claimed may lead to adverse reactions while lower percentages pave the way to treatment failure (Uddin et al., 2017). Dissolution is pharmaceutically defined as the mass transfer rate from a solid surface into the dissolution medium (Singhvi and Singh, 2011). According to British Pharmacopeia, Active Pharmaceutical Ingredient should be released from the tablet is not less than 70% of the stated amount within 45 minutes. Only one brand (M7 61.40%) failed to meet with BP limit while other brands passed the dissolution criteria. It could be due to defective formulation, compression pressure used, and binder effect (Akinleye et al., 2012). The dissolution of brands M3, M7, M12, & M15 were showed significant diferences compared to reference brand M2.

Among all quality parameters, uniformity of content, friability, and dissolution time were considered as official tests by British pharmacopeia. According to these official tests, out of 15 brands, nine brands (M2, M3, M4, M5, M10, M12, M13, M14, and M15) were within the pharmacopoeial limits. Since Metformin is a first-line drug used in diabetes treatment, the quality of Metformin is essential for its efficacy in controlling diseases. Treating with low-quality medicines could lead to therapeutic failure and progression of the disease. Special attention should be taken to imported medicines and ensure their quality before releasing to the market by relevant authorities.

IV. CONCLUSION

Among the tested brands of metformin hydrochloride, nine out of fifteen brands passed the all quality parametes according to British Pharmacopeia. Imported medicines should be strictly monitored for their quality.

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