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Original Article

COMPARATIVE *IN-VITRO* EVALUATION OF METFORMIN HCl AND PARACETAMOL TABLETS COMMERCIALLY AVAILABLE IN KANDY DISTRICT, SRI LANKA

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ABSTRACT

Objective: Availability of numerous brands of tablets with price variations compared to their generic drugs in the current drug market places health practitioners, pharmacists and patients in a dilemma of generic substitution. In such background, this study was aimed to compare the *in-vitro* efficacy of some of the low priced generic tablets with their brands commonly available in Sri Lanka.

Methods: A survey of the prices of commonly used tablets and capsules available at pharmacies in Kandy area in Sri Lanka was carried out. Based on the results of the survey, frequently used two tablets; Metformin HCl (one locally manufactured generic (M1) and 3 brands M2-M4) and Paracetamol (one locally manufactured generic (P1) and two brands P2-P3) were selected for the study. All the products were examined visually for their organoleptic properties and tested for uniformity of weight, disintegration time, assay value, dissolution rate, hardness or crushing strength and friability. Pertinent official guidelines were followed throughout all the tests.

Results: The results of aesthetic assessment showed no sign of defects and all the tested tablets complied with the official standards for the above parameters. Despite some minor differences in tablet hardness and disintegration time profiles, other *in-vitro* characteristics of the tested brands; Paracetamol and Metformin HCl and their locally manufactured generics appears to be similar and not significantly different from each other.

Conclusion: According to *in-vitro* official quality control tests, all the generics and brands of the respective drugs tested could be regarded as equally effective.

Keywords: Generic drugs, Brand named drugs, Metformin HCl, Paracetamol, *In-vitro* efficacy.

INTRODUCTION

There is a massive controversy about the efficacy of brand and generic drugs available in the market [1]. Generic drugs and brand-named drugs need to have exactly the same dosage, intended use, effects, route of administration, safety, and strength as the original/ generic drug [2]. In other words, their pharmacological effectiveness should be exactly the same, but may differ in peripheral features of pill color, shape, excipients such as binders or fillers and the specific manufacturing process [3]. Generic drugs are often cheaper than the brand-name versions, on average; the cost of a generic drug is 80 – 85% percent lower than the brand name product [4].

Regular laboratory tests of drugs in the market are crucial to maintain the quality of drugs, especially in developing countries where counterfeit and substandard drugs have become a major challenge to health care services [5]. Bioequivalence studies are vital to assist in substitution of brand with generics for affordability and therapeutic efficacy. There are two ways to conduct bioequivalence studies, *in-vitro* and *in-vivo*. As *in-vivo* tests are expensive and time consuming, *in-vitro* studies are widely used in post marketing and pre marketing quality control tests [6].

Main quality control tests (specifications are given in pharmacopeia) for tablets are weight variation, hardness, friability disintegration dissolution and assay [7 - 8]. Variation between tablets with respect to dose and weight must be reduced to a minimum. Uniformity of weight is an in process test parameter which ensures consistency of dosage units during compression. Any variation in the tablet weight obviously indicates a variation in the amount of active ingredient.

In general, tablets should be sufficiently hard to resist breaking during normal handling, packaging and shipping, and yet soft enough to disintegrate properly after swallowing. Hardness can directly affect the disintegration and dissolution. Therefore, hardness test is important as it determines the resistance to physical strength before usage.

Friability is a phenomenon where the surface of the tablet is damaged or shows a site of damage due to mechanical shock (ex: during transportation) [7 - 8]. It is the tendency of tablets to powder, chip, or fragment and this can affect the elegance appearance, consumer acceptance of the tablet, and also adds to the tablet's weight variation or content uniformity problems.

The first important step toward drug absorption is the breakage of tablets into smaller particles. Disintegration test is performed to find the time taken by tablets or capsules for complete disintegration. As tablets should disintegrate before dissolution, it is important for the evaluation of drug release. Tablets must disintegrate in the time set in the individual monograph. If one or more tablets failed to disintegrate, additional tests described by United States Pharmacopeia (USP) or British Pharmacopeia (BP) must be performed [7 - 8].

Dissolution test is a surrogate marker for bioequivalence tests as it is a practical and economical approach in developing countries where technology and resources are limited for *in-vivo* studies [9]. In the dissolution study, the release of active pharmaceutical ingredient (API) of drug product for the dissolution medium that is comparable to gastrointestinal tract fluid is determined. Based on this, *in-vitro* dissolution may be important in assessing *in-vivo* performance of drug absorption [10 - 11].

The API is the chemical that has the desired biological effect. There may be many ingredients in a tablet, for example, diluents, binders, disintegrants, thickening agents, glidants, colorants, sweetening agents, but the API is the ingredient concerned for the therapeutic effectiveness. Most dosage forms are designed to deliver the API to the site of action [12]. It is important to know if there are variations in the percentage content of active ingredients. This can be detected through an assay test. The percentage content of active drug should be routinely measured to check whether a tablet contains a proper amount of drug [7 - 8].

Some research studies have revealed that brand name drugs are more efficacious than generic drugs [13-15] while others have shown that there was no distinction between brand and generic drugs [16-20]. In Sri Lanka, there was no previous studies (*in-vitro*) reported on the quality of the higher priced brand and locally manufactured low priced generic drugs prescribed for common prevalent disorders.

The main objective of this study was to evaluate the quality (*in vitro*) differences of locally manufactured generics and high priced brands available in Sri Lanka. Metformin hydrochloride (Metformin HCl); the first-line drug for the treatment of type 2 diabetes (Non-Insulin Dependent Diabetes Mellitus, NIDDM) [21] and Paracetamol; general analgesic [22], were chosen as model drugs for the study as these two medicines are fast moving and highly consumed by Sri Lankans and also having significant price differences among brands.

MATERIALS AND METHODS

Materials

Three different brands of Metformin HCl 500mg and two different brands of Paracetamol 500mg were purchased from a registered pharmacy at Kandy. Respective generic drugs were purchased from other two registered pharmacies at Kandy. The selected Metformin HCl generic product was coded as M1 and brands were coded as M2, M3 and M4. Generic Paracetamol was coded as P1 and its brands were coded as P2 and P3. The study was performed within product expiration dates. The reagents used were potassium dihydrogen phosphate orthophosphate (Merck Specialities' (PVT) Ltd, India) and sodium hydroxide (Lobachemie (PVT) Ltd, India).

Equipment

USP II (paddle Type) dissolution test apparatus (Digital Tablet Dissolution Test Apparatus Model: LDA-6D, Lasany International, India), UV Spectrophotometer (Model: GENESYS 10S UV-Vis, Thermo Fisher Scientific, P. R. China), Electronic Analytical Balance (Pioneer TM Balances, Ohaus Corperation, USA), pH Meter (Handheld pH /mv/Temperature Meter, IQ140, IQ Scientific Instruments,Inc, USA) Magnetic Stirrer (Model: 1MLH, SR No: DBMS-1833, Rajendra electrical Industries Ltd, India), Digital tablet disintegration test apparatus (Model: LTD-DV, Lasany International, India), Hardness Tester (PHARMA TEST Company, Model: PTB511E, Germany), Friability Tester (PHARMA TEST COMPANY, Model: PTF10E, Germany) were used for the analysis.

Methodology

Survey on prices of generic and brand medicines

Prices of commercially available drugs were observed from 10 pharmacies in Kandy District, Sri Lanka.

In-vitro quality control tests on selected brand and generics

The study was carried out in the time between July to October 2013 at Pharmaceutical Laboratory and Pharmaceutical and Instrumentation Laboratory in Department of Pharmacy, Faculty of Allied Health Sciences, University of Peradeniya, Sri Lanka. One generic and three brands of Metformin HCl and a generic and two brands of Paracetamol with significant price differences were selected.

Aesthetics tests

Color, shape, luster, nature of the surface (smooth or rough) of the tablets from each brand and generic were examined visually.

Weight variation

Twenty tablets were selected randomly and weighed individually. The weight was calculated and individual weight was compared to the average weight. The percentage deviation of each tablet was calculated as the formula below.

$$\text{Percentage Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

The tablet passes the test according to BP if not more than two of the individual weights deviate from the average weight by ± 5% and no-one deviates by ± 10 %.

Hardness test, thickness and diameter of the tablets

Randomly selected 10 tablets were placed between the jaws of the hardness tester individually. Thickness and diameter of tablets from each brand and generic were also measured by the same apparatus. After inserting the approximate thickness and diameter values of the tablets, the accurate values of those parameters were measured. The pressure at which each tablet crushed was recorded according to BP 2012 specifications. The average crushing strength /hardness values were reported in Newton (N).

Friability test

According to BP 2012, Twenty (20) tablets from each sample were dedusted, weighed and placed in the drum of friabilator and subjected to 100 revolutions (25 rpm × 4 mins). The tablets were then again dedusted and weighed and percentage (%) loss was determined using the formula given below.

$$\text{Percentage Friability} = \frac{W0 - W1}{W0} \times 100$$

Where W0 and W1 are initial and final weights respectively

The sample passes the test if a percentage loss is not more than 1% of the weight of the tablet tested.

Disintegration test

The disintegration time of randomly selected six tablets of each sample was determined at 37+2^{0}C in distilled water using disintegration apparatus, according to BP specifications. The machine was set to 30 rpm. The disintegration time was taken to be the time no granule of any tablet was left in the mesh.

Dissolution test

Dissolution test was conducted according to the specifications on BP 2012.

Dissolution test for Metformin HCl tablets

The dissolution rate of Metformin HCl tablet was studied using USP II (Paddle type) digital tablet dissolution test apparatus employing a paddle stirrer at 100 rpm using 900 ml of pH 6.8 potassium dihydrogen phosphate orthophosphate buffer at 37.0 ± 0.5^{o}C as dissolution medium. Test time was 45 minutes. Absorbance of the resultant solution was then determined by UV-Visible (Ultra-Violate visible) spectrophotometer at 233 nm. The total content of Metformin HCl ($C_4H_{11}N_5$. HCl), dissolved in the medium was calculated taking 806 as the value of *A* (1%, 1 cm) at the maximum at 233 nm. The Procedure was repeated for each brand and the generic tablets. The average amount of dissolved active ingredients was calculated.

Dissolution test for Paracetamol tablets

The dissolution test was undertaken using USP apparatus II (paddle type) in six replicates for each brand and generic. The medium was pH 5.8 phosphate buffer rotating at 50 rpm and at the temperature of 37.0 ± 0.5 ^{0}C. After the test time of 45 minutes, 20 ml of the samples from each vessel was withdrawn. The filtrate was suitably diluted and absorbances of the resultant solutions were then determined by UV-Visible Spectrophotometer. The total content of Paracetamol ($C_8H_9NO_2$) dissolved in the medium was calculated by taking 715 as the value of A (1%, 1 cm) at the maximum at 257 nm.

Assay test

The assay tests for the two drugs were done in line with the specifications of BP 2012. Each test consisted triplicates and test was repeated 3 times for each sample and average assay values were calculated.

Assay test for Metformin tablets,

Initially twenty tablets were weighed using analytical balance and average weight was taken. Tablets were then powdered using mortar and pestle. Powder equivalent to 0.1g of Metformin HCl was then stirred with 70 ml of distilled water for 15 minutes using a

magnetic stirrer. The resultant solution was diluted to 100 ml with distilled water and filtered. The filtrate was then suitably diluted and absorbance of the final solution was measured by UV-Visible spectrophotometer, taking 798 as the value of A (1%, 1 cm) at the maximum at 232 nm.

Assay test for Paracetamol tablets

The average weight of twenty tablets was recorded using an analytical balance. Tablets were then powdered and powder equivalent to 0.15g of Paracetamol was weighed. It was mixed with 50 ml of 0.1M Sodium Hydroxide (NaOH) and diluted with 100 ml of water. The resultant solution was stirred for 15 minutes by magnetic stirrer and sufficient amount of distilled water was added to produce 200 ml. The solution was then mixed, filtered and suitably diluted. Absorbance of the final solution was measured taking 715 as the value of A (1%, 1 cm) at the maximum at 257 nm.

Statistical analysis

Microsoft-Office Excel was used in the data analysis. The results were expressed as mean and standard deviation.

RESULTS

Table 1 shows the evaluated physicochemical parameters of brands and generics of Metforn HCl tablets.

Table 1: Evaluated physicochemical parameters of different types of Metformin HCl tablets

Parameter	Product code			
	M1	M2	M3	M4
Thickness (mm) (M+/-SD)	6.12 +/- 0.049	5.36 +/- 0.038	6.04 +/- 0.053	5.77+/- 0.136
Diameter (mm) (M+/-SD)	11.54 +/- 0.046	12.91 +/- 0.021	11.02+/- 0.005	11.07+/- 0.014
Weight Variation (M+/- SD)	0.61+/- 0.006	0.63+/- 0.012	0.56+/- 0.008	0.53 +/- 0.010
Hardness (N) (M+/- SD)	81.60 +/- 7.23	51.00+/- 2.59	102.80+/- 11.14	122.1+/- 23.23
Disintegration Time (min) (M+/- SD)	6.44 +/- 0.311	3.44 +/- 0.040	5.25 +/- 0.050	7.17 +/- 0.042
Dissolution (%)(M+/- SD)	96.40 +/- 2.06	97.63 +/- 2.88	93.65 +/- 3.88	97.82 +/- 2.40
Assay (%) (M+/- SD)	101.40 +/- 3.38	102.44 +/- 2.93	97.52 +/- 1.78	98.25 +/- 2.04

M- Mean, SD- Standard Deviation

For Metformin HCl tablets

Innovator of metformin [23] (M4)is 12 times more expensive than the locally manufactured generic (M1) and imported brand (M2). M3 is about 5 times more expensive than the generic. The visual inspection of local and imported brand products showed no sign of defects in all tested tablets. For Metformin tablets, M4 had the highest crushing strength of all the four types with hardness of 122.10N and M2 had the lowest hardness of 51.00 N. M1 had the maximum thickness, while M2 had the minimum. M2 had the maximum diameter, while M3 had the least diameter of tested samples. As Metformin HCl tablets are film coated, friability test is not applicable. By being below the specified percentage deviation according to BP 2012, all the tested metformin tablets passed the weight variation test. The highest disintegration time (7.17 minutes) was observed for M4 tablets, when the minimum disintegration time was reported for M2 tablets with 3.44 minutes.

The average dissolution for Metformin HCl was ranging from 93.65% to 97.82%. The mean assay of all the generic and brands of Metformin HCl tablets was in conformity with the BP requirement, in the range 97.52 %–102.44 %. The assay of all the generic and brands of Metformin tablets was in conformity with the BP requirement, in the range of 95.79 %–97.43 %.

For Paracetamol tablets

Table 2 shows the evaluated physicochemical parameters of brands and generics of Paracetamol tablets.

Table 2: Evaluated physicochemical parameters of different types of Paracetamol tablets

Parameter	Product Code		
	P1	P2	P3
Thickness (mm) (M+/-SD)	4.11 +/- 0.022	5.23 +/- 0.026	5.25 +/- 0.071
Diameter (mm) (M+/-SD)	12.57 +/- 0.005	7.25 +/- 0.009	7.38+/- 0.015
Weight Variation (M+/- SD)	0.56+/- 0.005	0.58+/- 0.002	0.56+/- 0.005
Hardness (N) (M+/- SD)	152.10 +/- 6.66	477.70+/- 21.47	239.40+/- 9.92
Friability (%)	0.16	0.94	0.15
Disintegration Time (min) (M+/- SD)	1.13 +/- 0.015	2.07 +/- 0.064	4.14 +/- 0.025
Dissolution (%) (M+/- SD)	98.39 +/- 1.28	100.61 +/- 0.74	99.31 +/- 1.43
Assay (%) (M+/- SD)	97.43 +/- 1.60	96.23+/- 1.22	96.32 +/- 1.40

M- Mean, SD- Standard Deviation

P3 is about 3 times more expensive than the generic tablet, while P2 is 2.5 times more expensive. The visual inspection of local and imported brand products showed no sign of defects in all tested tablets. Paracetamol tablets (compressed) P2 had the highest hardness value with 477.70N and the lowest from P1 that was 152.10N. P3 had the maximum thickness, while P1 had the minimum. P1 had the maximum diameter due its round shape. P2 had the least diameter of tested samples. P2 had the highest percentage friability of 0.94%w/w and minimum friability was for P3 tablets.

As there are no tablets outside the limit, all the tested batches of all Paracetamol tablets passed the weight variation test. The highest disintegration time (4.14 minutes) was observed for P3 tablets, while minimum disintegration time was 1.13 minutes for P1 Paracetamol tablets. Paracetamol tablet dissolution in 45 minutes ranged from 98.39% to 100.61%.

DISCUSSION

This study was aimed to survey generic and brand tablet products present in the Sri Lankan market according to their price and to evaluate their quality according to standards of official pharmacopeia in order to identify the products that are interchangeable.

The Ministry of Health and CDDA (Cosmetics, Devices and Drug Regulatory Authority) are the regulatory authorities in Sri Lanka that grant marketing authorization for branded and generic drug

products. According to the current regulation a product has to satisfy the compendia requirements for safety, purity and quality according to the standards[24].

Additionally, either drug is sold under the generic name or brand name, quality control studies and evidence of bioequivalence studies are required to show that the generic is bioequivalent to the official drug, according to the US FDA (United States Food and Drug Administration) and the European Medicines Agency [25]. Only pharmaceuticals that comply above requirements are registered by CDDA of Sri Lanka.

According to the survey carried out, higher price variations among generic and brand drugs were observed. This may due to research and development add expenses. Pharmaceutical manufacturers are mostly profit driven companies, therefore aiming to earn more profit they may sell their products at higher prices. Cost of advanced technology, equipment and machines may lead some medicines to be higher priced than others. Cost of packaging materials and excipients also add expenses to the medicinal products.

All the tablets were inspected visually for the color, shape and the presence of black spots or breached edges. They were assessed for general organoleptic properties and any sign of imperfections. In fact, these features are essential for consumer preference and batch to-batch uniformity. The results of aesthetic assessment showed no sign of defects in all tested tablets.

Tablets greater than 250 mg should have a percentage deviation in weight less than 5% (B. P 2012) Results of weight variation test showed that all the brands complied with the compendial specification for uniformity of weight. Uniformity of weight does serve as a pointer to Good Manufacturing Practices (GMP). During the granulation and compression stages; large intra batch variations in tablet weight and the amount of API in the formulation can be occurred [17]. The strict adherence to GMP ensures uniformity of tablets' weight.

Crushing strength or hardness test shows the ability of tablets to withstand pressure or stress during handling, packaging and transportation. High tablet strength should not compromise disintegration in the stomach. If the tablet is too hard, the disintegration time is long and cannot meet up the dissolution specification. Tablets should disintegrate within the time limit prescribed by the BP, if it is too soft, it cannot withstand handling when dealing with processes such as coating, packaging and shipping operations. The harder the tablet, the less friable and the more time it takes to disintegrate. Even though there is not a standard hardness value, oral tablets having hardness of 40N is considered to be the minimum for satisfactory tablets [27]. Results for the metformin HCl tablets (film coated) indicated that all the (M1, M2, M3 & M4) tablets were complied the crushing strength/hardness test. Brand M4 had the highest crushing strength of all the four brands while M2 had the lowest hardness. For Paracetamol tablets (compressed) all the tablets tested (P1, P2, P3) passed the test. P2 had the highest hardness value and the lowest was from P1.

In general, if the tablet hardness is too high, its disintegration has to be checked before rejecting the batch. And if the disintegration is within limits, the batch will be accepted and dissolution profile will be checked. The results proved that all the tested tablets had impressive friability values. Even though P2 had the highest hardness value (477.70 N), it gave the highest percentage friability (0.94%). This may be due to its' high percentage weight loss after tumbling as a result of poor compaction of the outer core of the tablet despite of the higher hardness of the inner core.

According to the limit, no compressed tablets, batch should have a friability value of greater than 1.0%w/w, because if powder loss is greater than 1.0% w/w, it is directly lowering the assay value of the tablet therefore results less therapeutically effective tablets. However, when capping of tablets and cracked, cleaved or broken tablets are observed during friability testing, the tablet product is rejected regardless of the percentage weight loss [7]. Such deformations were not observed for any of the samples tested.

All the samples passed the BP specifications for disintegration rate test. The disintegration rates for film coated Metformin HCl was ranged from 3.44 to 7.17 minutes, indicating that all the disintegration times were within the BP limit of 30 minutes. For all un-coated Paracetamol tablets, it was ranging 1.13 to 4.14 minutes and therefore within BP limits of 15 minutes.

In tablets, the surface area of contact between the solid and liquid in the dissolution process determines by the disintegration in to a larger extent and could be the rate-determining step in the process of drug absorption [28]. It is an important step because the rate of disintegration affects the dissolution and subsequently the therapeutic efficacy of the medicine.

Dissolution testing of solid oral drug products has emerged as one of the important control tests for assuring product uniformity and batch-to-batch equivalence. The effectiveness of tablet dosage forms relies on the drug dissolving in the fluids of the gastrointestinal tract prior to absorption into the systemic circulation. Drugs with poor dissolution profiles will not be sufficiently available in the body system to produce the desired therapeutic response [29]. The rate of dissolution of the tablets or capsules is therefore crucial.

According to dissolution tests, the release of Paracetamol and Metformin HCl in simulated gastric fluid from all generic and brands was greater than 90%. As per the specifications, limit should be greater than 80%. All the tablets passed the dissolution test, implying that they are likely to exhibit good bioavailability and thus give good therapeutic responses. Therefore, required absorption of drug can be assured.

The aim of a formulation is to introduce API to the body effectively, which is indicated as medicines to cure or prevent diseases. If the formulation has a lower percentage of API, it may fail to meet the therapeutic response and if it has a higher percentage of drugs than it claimed, that leads to toxicity and adverse reactions. Therefore, the content of active ingredients should remain within the upper and lower limits specified by the respective pharmacopoeia. The limit for the assay value given in BP for both drugs is 95%-105%. The result ascertains the tablets analyzed in this study passed the assay test according to BP specifications. Assay values of all the Metformin tablets were within the range of 97.52% to 102.44% of the stated amount of Metformin HCl. For Paracetamol Tablets it was within the range of 95.79% to 97.43%.

Generally there should be a good balance between the physical properties and release properties of tablets. Even though the brands of Metformin had relatively high crushing strength (>80N-M1, M3 and M4) their disintegration times was less than 10 minutes. On the other hand, M2 had minimum disintegration time (3.44 minutes) ensuring impressive release properties. All these properties depend on the production process and the chemical properties of all ingredients in the formula.

Brands M1, M2 and M3 showed faster disintegration time (< 7 minutes) but relatively slower dissolution rates in comparison to the innovator brand, M4. This shows that the disintegrated particles may have retained the active drug within their hard core and did not release the drug into the dissolution medium as freely as innovator brand.

When all the tablet properties are considered, all the generic and brand versions of Metformin HCl comply with quality standards. Also, quality standards of all the tested Paracetamol tablets were not significantly different to each other. Therefore, according to *in-vitro* tests, this study shows that the price variation of the tablets tested may not due to the quality of the product. However packaging materials, excipients and the quality of ingredients used in all these tablet formulas may not be the same. Therefore, stability and side effect profiles may vary.

CONCLUSION

When all the tablet properties are considered, all the generic and brand versions of Metformin HCl comply with official *in- vitro* quality standards. Also, quality standards of all the tested Paracetamol tablets were not significantly different to each other.

Even though there are price variations among the tablets, all the tablets tested are equally complying with *in-vitro* standard specifications and therefore fulfilling the legal requirements for patient use. Furthermore, *in-vivo* bioequivalence studies for generic and brand drugs are required to be conducted to ascertain more precise therapeutic and clinical equivalence.

CONFLICT OF INTEREST

Declared None

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