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QUALITY CONTROL ASSESSMENT OF LOCALLY MANUFACTURED ASPIRIN TABLETS IN COMPARISON TO GLOBALLY PRODUCED GENERICS

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ABSTRACT

Challenges confronting the locally manufactured medications in Saudi Arabia have been increasing in the last decade. The Saudi market is mainly built on imported medications. Meanwhile, local manufacturers are much neglected in the Saudi's market. Building consumer's trust for local medication is one of the main targets to achieve success in decreasing the rate of importing medication while increasing locally produced ones. This study aims to compare the quality of some of the marketed low dose enteric coated Aspirin tablets (as a model product) produced by local Saudi pharmaceutical companies (F1 and F3) with others manufactured by an Arabian Emirate company (F5), and two other brands of USA companies (F2 and F4) as global generics. F2 represents the proprietary product produced by Bayer (Bayer Aspirin ®), to which all other brands were compared. Different quality control tests adopted by the United States Pharmacopeia and/or the British Pharmacopeia were applied to the five brands. Tablets were also assessed for physical and organoleptic properties. Results revealed that nearly all of the tested tablets met the requirements of the quality control tests adopted. This reflects their equivalency both pharmaceutically and statistically.

KEYWORDS: Aspirin, Acetylsalicylic acid, Enteric coated, Evaluation, Quality control

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INTRODUCTION

Saudi Arabia is one of the world's largest markets for medical products and equipments. In recent years, consumers have taken greater interest and responsibility for their own health. They are not only basing medication purchases on price, but they are also concerned about where their drugs come from, and the variability of the raw materials used. Consumers prefer imported medications, building their choice on trust in the internationally manufactured generic products. Approaches based on comprehensive and integrated concepts can also help us to meet the challenges of the drastic increase in the need for the imported medications over the locally manufactured ones. For such achievement, we must gain consumers' trust by ensuring uniformity in standards of quality, efficacy and safety of pharmaceutical products. Reasonable assurance has to be provided that global products containing the same active ingredients as local manufactured ones are clinically equivalent. All categories of the government and civil society, including pharmacy institutes must cooperate to regain the consumer's trust. One of the main concerns of any government is to develop an organized mechanism for adjusting the prices of locally manufactured generics. This process in turn, will serve on providing the consumer with reasonable priced product while in the meantime preserving competitiveness of this industry. In addition, we must put in mind that the export price of any medication includes several items related to the transportation, bank charges and insurance that must be added to the final cost price that the consumer will have to be loaded with. Aspirin is one of the most frequently used drugs as an analgesic, anti-inflammatory, antithrombotic and antipyretic agent [1]. On the other hand, non- steroidal anti-inflammatory drugs (NSAIDs) including ketoprofen and others are also being frequently used and prescribed as an over the counter medications for their antipyretic, analgesic and anti- inflammatory effects, despite many reports of severe side effects of long term use [2]. Low dose Aspirin tablets are effectively used as anti-platelet agents for the prevention of cardiovascular disease [3]. It irreversibly inhibits platelet cyclo- oxygenase, resulting in a decrease in the formation of thromboxane (Tx) A2 and Tx A2-induced platelet aggregation [4]. However, one of the main adverse effects produced by aspirin is gastrointestinal disturbances, which can lead with long term use to gastritis or even ulceration of the gastric mucosa [5]. These complications of aspirin result from the salicylic acid produced during the hydrolytic procedure of the acid labile acetylsalicylic acid in the acidic gastric environment [6]. The use of enteric coated aspirin tablets as an alternative to the use of NSAIDs has been suggested with the benefit of lower prices as well as higher safety [7]. Enteric coating of a solid dosage form is a well established approach to prohibit the drug release in the acidic environment of the stomach and permit its release in the alkaline pH of the small intestine [8]. This process either protects the acid-labile drugs from degradation in the stomach or protects the stomach linings from the corrosive action of some drugs [5]. pH-dependent polymers used generally for enteric coating probably contain carboxylic acid groups. Their un-ionized form in an acidic pH environment of the stomach prevents their disintegration while the higher pH of the small intestine promotes their dissolution and the drug is consequently released [9]. The objectives of the present study were to provide a closer look at the possible differences between generics locally manufactured and compare them to internationally produced ones. Assessment of the quality of the enteric coated tablets according to the USP and BP includes content uniformity, disintegration, and dissolution tests. Other characterizing tests performed in the study include physical characterization of tablets, determination of tablets' thickness, hardness, and friability [10, 11], to ensure the pharmaceutical quality of the investigated brands.

MATERIALS AND METHODS

Five Commercial Aspirin enteric-coated tablets (81mg) were purchased from either Saudi Arabian market (two are manufactured by Saudi Arabian companies, and one of an Emirate's company), or from USA market (manufactured by two international drug industries). All other chemicals and reagents were of pharmaceutical or analytical grade.

(i) Determination of the physical and organoleptic properties of the tablets

The different physical and organoleptic characteristics were determined including general appearance; shape, odor and color.

(ii) Determination of uniformity of weight and content uniformity

Twenty tablets were weighed individually (X_1, X_2, X_3… X_{20}) using a sensitive balance (METTLER, TOLEDO b 204-S, Switzerland). The average weight of tablets was calculated applying equation 1. Standard deviation was also calculated.

$$x = \frac{Total\ weight\ of\ tablets}{Number\ of\ tablets} \qquad Equation\ 1$$

According to the USP, "The requirements for uniformity are met if each individual tablet is within 85% to 115% of the mean" [10]. On the other hand, according to the BP in the test for uniformity of weight of tablets, "not more than two of the individual weights (of 20 tablets) should deviate from the average weight by more than 7.5 % deviation for tablets weighing >80 - < 250 mg [11]. For uniformity of drug content, ten tablets are individually assayed for their content, where each tablet was crushed in a mortar and dissolved thoroughly in 100ml volumetric flask using phosphate buffer pH 6.8. Suitable dilutions were made and the solutions were determined spectrophotometrically (Spectrophotometer, Apel PD- 303UV, Japan) at λ 265nm. The requirements for content uniformity are met if the amount of the active ingredient in each tablet lies within the range of 95-105 % of the label claim.

(iii) Disintegration test

A 1000 ml beaker was filled with 750 ml 0.1N HCl and the temperature was adjusted at 37±2º C. Six tablets were placed into the basket-rack of the disintegration apparatus (Automatic disintegration tester, Logan, Co.) for 2hr for a positive test, after which no signs of disintegration, cracking or softening must be seen. This step is followed by addition of 250 ml Phosphate buffer to maintain the pH at 6.8 for 30 min, during which the tablets disintegrate completely.

(iv) Dissolution test

Dissolution studies were performed using USP XXIII dissolution apparatus II paddle type (Dissolution Apparatus, Erweka, Germany) in 1000 ml medium at 37.0±0.50C, at a rotation speed of 100 rpm. Dissolution media selected were 750 ml 0.1N HCl (pH 1.2) for the first 2 hours and phosphate buffer (tri- sodium phosphate), 250ml to adjust the pH 6.8 after. Five milliliters sample was withdrawn at specific intervals and replaced with a fresh dissolution medium. These samples were filtered using a 0.45 µm membrane filter. The concentration of samples was analyzed using UV spectrophotometer (Spectrophotometer, Apel PD- 303UV, Japan) at λ 280nm and λ 265 nm for acid and alkaline pH respectively. The dissolution profiles were compared for their pharmaceutical equivalence to the innovator product profile applying different methods including [12,13] %Dissolution efficiency $_{t\,240}$ (% DE $_{t\,240}$), Mean Dissolution time (MDT), Mean Residence Time (MRT), similarity factor (f2) and difference Factor (f1), by the use of a software program Double Dummy Solver, DD- solver. Statistical comparison was also done for each brand in comparison to the innovator product applying the Student t-test using Microsoft excel program.

(v)Friability test

Ten tablets were weighed on an accurate analytical balance. The tablets were placed in the friability tester (Friability tester, Pharma Test, PTFE D-63512, Germany) and rotated 100 times (25rpm x 4). The tablets were smoothly brushed from any dust and re-weighed. According to USP [10], the tablets should not lose more than 1% of their total weight calculated according to equation 2

$$\%\ Loss = \left(\frac{initial\ weight - final\ weight}{initial\ weight}\right) \times 100 \qquad Equation\ 2$$

(vi) Tablet thickness and Diameter

Tablet thickness is important for tablet packaging as very thick tablets will affect packaging either in blisters or cans. Tablet thickness and diameter is measured by means of Micrometers.

(vii) Tablet hardness

Using forceps, 10 tablets were individually adjusted between the platens of the hardness tester (ERWEKA® GmbH, TBH210). Starting the instrument, a visual reading of tablet hardness was detected at the point of break. The mean hardness for each brand was calculated with its mean standard deviation.

RESULTS AND DISCUSSION

Five brands of enteric coated low dose aspirin tablets were purchased from either Saudi Arabian or USA community pharmacies. The tablets under study were subjected to a complete evaluation for different physical characteristics, organoleptic properties, Compendial and non- Compendial quality control tests. Results of the different physical and organoleptic properties of the tablets investigated are shown in Table I.

Table I
Organoleptic and characteristic properties of Aspirin tablets

Parameter	Code of Formulation				
	F1	F2	F3	F4	F5
Color	Dark Orange	Pale Yellow	Yellow	Pale Orange	White
Shape	Round	Round	Round	Round	Round
Odor	nil	nil	Slight acetic acid odor	nil	nil
Diameter (mm ± S.D.)	6.16	6.5	7.2	7.4	7.1
Thickness (mm± S.D.)	3.3	3.1	3.7	4.4	3.1
Weight variation (mg ± S.D.)	112.7 ± 2.6	104.6 ± 2.7	168 ± 3.2	203.8 ± 3.8	118.2 ± 4.2
Disintegration time in 0.1NHCl, pH1.2 (min)	Pass	Pass	Pass	Pass	Pass
Disintegration time in phosphate buffer pH 6.8 (min)	4~ 14	8 ~ 13	9~ 10	3~ 4	4~20 except one failed
Friability test % weight loss	0	0.29	0	0	0.025
Hardness (Kg force)± S.D.	7.85± 0.673	4.89± 0.441	10.91± 0.718	14.68± 0.881	5.3± 0.127

All the commercially tested tablets showed acceptable appearance and organoleptic properties except F3, which had a slight acetic acid odor indicating slight hydrolysis of the active ingredient. In a previous study of the process of hydrolysis of acetylsalicylic acid from the generic Bufferin 81-mg tablets, aspirin was found to undergo gradual decomposition into salicylic and acetic acid in the presence of moist air. It is also indicated that this product should be well packed in aluminum-sheet package to ensure its intactness [14]. However, it is worth noting that F3 was packed in a bottle of 40 tablets and might have been subjected to the entrapment of some moisture during preparation or packaging that caused the start of hydrolytic process of aspirin. Although tablets of the different companies had the same amount of labeled drug (81mg), yet they differed in their total weight of the individual tablets which ranged from about 105 to 204 mg. Figure 1 shows the results of the average uniformity of weight for the five aspirin products. It was noted that all the

deviation from the average weight in each product didn't vary in all cases by more than 7.5% (according to the BP specifications) [11] except for F5 product, where only one tablet passed the permitted range, compared to all other formulations which successively passed the test. On the other hand, according to the USP pharmacopeia, all products passed the test as their individual weights were in the range of 85- 115% of the mean weight [10].

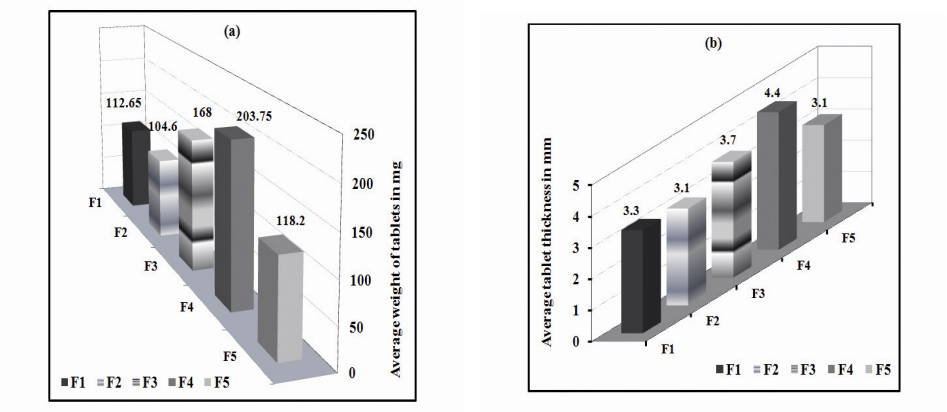

Figure 1
a. Comparison of different brands weight variation
b. Comparison of different brands thickness

Tablets' diameter and thickness were measured (Table I) using a micrometer. The results revealed that the tablets' diameter of the five products ranged between 6.2 and 7.1mm and their thickness ranged between 3.1 and 4.4 mm (Figure1). These differences between generics in weight, diameter and thickness probably depended on the added adjuvant in different amounts according to each company's formulation and the coating layer applied in the different products [15]. The result of drug content test was as follows: the mean of drug content of the tested tablets of F1, F2, F3, F4, and F5 were 82.5mg ± 1.04, 83.96 mg± 0.27, 84.24± 1.4, 85.47± 1.08 and 83.24± 2.83 respectively. Since the USP limit of the labeled amount of aspirin to be ranging between 95 and 105% (represented in a minimum of 76.95 and a maximum of 85.05mg). The results indicate that the requirement were met for all brands according to the official USP specification, although in one case, F4 was on the higher borderline for drug content. This is probably due to the presence of adjuvant in the tablet's formulation that interfered with the spectrophotometric readings, which calls for a more sophisticated process of analysis. One of the very effective tests indicating the compactness of tablet's core and coat is the friability test, which serves to supplements other physical strength measurements, such as the tablet breaking force. Results of this test as shown in Table I reveal that all tablets under study met the USP specification, as the maximum mean weight loss from the three samples taken was not more than 1.0%. The tablets must be hard enough to withstand mechanical stress during packaging, shipment, and handling by the consumer. All products under study were subjected to the hardness test as stated under the methodology section. The results listed in Table I and shown in Figure 2 revealed that the order of increasing hardness in terms of Kg force was as follows: F2 (4.88 kg) □ F5 (5.3 kg) □ F1 (7.85 kg) □ F3 (10.91kg) □ F4 (14.68 kg).

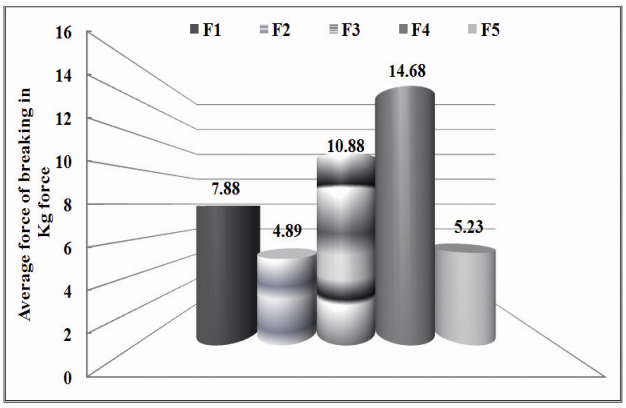

Figure 2
Comparison of different brands hardness

This ascending order is somehow in agreement with the tablet weight, diameter and thickness, where F4 tablet had the biggest value of weight, diameter and thickness and thus needed more force to breakup. However, F2 had the smallest weight and intermediate diameter, but, on the other hand had the smallest thickness which could have contributed to its lower value of hardness. It is worth mentioning that formulation parameters have been identified to influence tablet characteristics. Variations in the manufacturing process could be the main factor in the differences seen in the tablets, hardness, disintegration and dissolution rates between the different brands [16]. All the commercial brands passed the test for disintegration in 0.1N HCL. *In vitro* disintegration of commonly enteric coated tablets reportedly happen within 30 min in pH 6.8 phosphate buffer [5, 17]. All tablets under study passed the test in alkaline medium (phosphate pH 6.8) except F5 tablets, where one of the six tablets of F5 product failed to disintegrate within 30 min. It was observed that within the same batch, F5, the disintegration time varied and ranged from 4 to 20 min in buffer pH 6.8 which can be considered a wide range comparing it to the other brands. This can be explained by the possible technical error in the coating procedure of the tablets where some tablets received an extra coating with the subsequent failure of disintegration at the required time . Drug release from the enteric coated aspirin tablets was also investigated. The release profiles from the tablets are shown in Figures 3. There was no drug release in 0.1N HCl for 2h indicating the enteric coat intactness and resistance to disintegration at this pH. However, drug release started immediately from all aspirin brands after the alteration of the pH to be 6.8 using the phosphate buffer.

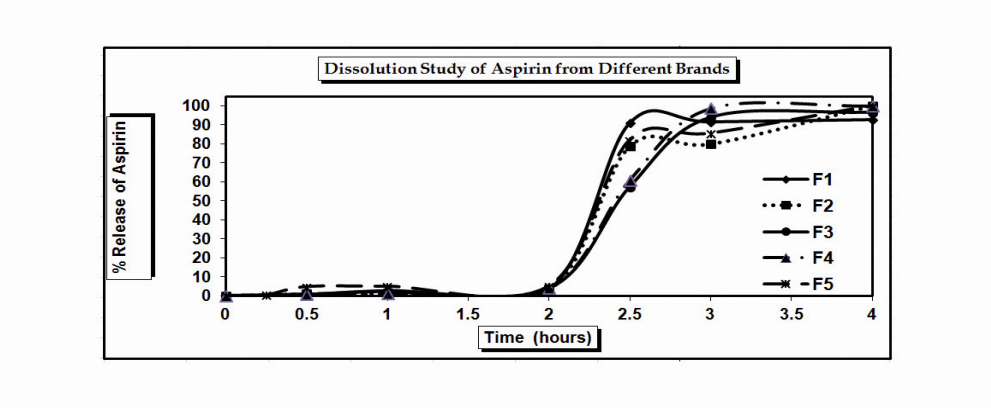

Figure 3
Comparative release profiles of enteric-coated aspirin tablets of different brands in pH 1.2 0.1N HCl for 2 h and subsequent pH 6.8 phosphate buffer

The above figure showed that F1, F2 and F5 released about 80% or more of the total drug in the first half hour in alkaline medium. On the other hand, F3 and F4 released the drug in a slower pattern, where only about 60% were released in the first half hour in alkaline pH. This could be attributed to the differences in the adjuvant added and techniques applied in the formulations from one company to another. However, by the end of the first hour in pH 6.8, all formulations showed a comparable pattern of drug release till the end of test where nearly all formulations released from 90 to 100% of the labeled drug. Table II shows the comparative dissolution parameters used in this study. It is clear from the results that all tablets under study had a similarity factor value above 50 when compared with the innovator product, indicating similarity in the release pattern [12, 13]. However, formulation F5 was more pharmaceutically equivalent to the innovator (f2=73.5), followed by F1 (f2=57.9). On the other hand the least similarity factor was calculated for F3 and F4. Same results were observed on calculating the difference factor, f1 where F5 and F1 showed the lower values in dissimilarity [12, 13]. Nevertheless, on calculating the % $DE_{t\ 240}$, MDT and MRT, they were all comparable to each other with respect to the innovator (F2).

Table II
Comparison of Dissolution parameters

Parameter	F1	F2*	F3	F4	F5
% $DE_{t\ 240}$	41.31	38.36	38.09	39.62	41.31
MDT	2.22	2.47	2.42	2.42	2.35
MRT	1.22	1.28	1.28	1.22	1.24
f1	11.41	-	16.02	14.07	6.38
f2	57.87	-	50.26	50.27	73.53

** F2 represents the innovator product*

Statistical analysis using the Student t-test analysis of the dissolution parameter showed no significant difference ($p > 0.05$) among each brand when compared to the innovator (F2). They all indicated similar statistical behavior in their dissolution profiles (p values calculated were 0.193, 0.477, 0.498 and 0.459 for F1, F3, F4 and F5 respectively). Moreover, on comparing the five release profiles using One-Way ANOVA test, the p value was calculated to be 0.9915 indicating a non significant difference within all five generics at $p > 0.05$

CONCLUSION AND RECOMMENDATIONS

Quality control tests are crucial in the pharmaceutical field, as they ensure that the final products follow the official international standards. Compendial and non Compendial tests have been traditionally used to determine and compare the quality of the prepared dosage forms of different brands. Using these tests, we conclude that the local Saudi Arabian manufacturers of the tested tablet products met the official required international standards. On comparing those to other globally manufactured brands, or with that related to other Arabian company, the data obtained showed that they were pharmaceutically equivalent and can be used as alternatives to any of the global brands with no difference in their qualities. The outcomes obtained from this study may act as the first step in proving the quality of our products and promoting confidence in our pharmaceutical industries. However, some approaches must be taken by the pharmaceutical related personnel to insure that the consumers would have the same confidence shown in purchasing international pharmaceuticals. Simply by encouraging similar quality control studies to compare local products to their counterparts from multi sources, evidence can be generated to assure consumers of the matching quality. Additionally, the data obtained from such studies should be published in peer review specialized journal, conferences, and through other related public media such as newspaper, TV…etc. This will raise the awareness of our

local consumers towards the national products both as reliable and qualified alternatives to the imported generics.

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