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Appraisalment of Ranitidine Hydrochloride Tablets From Selected Companies in the Local Sudanese Pharmaceutical Market

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ABSTRACT

Ranitidine hydrochloride tablet is used as a drug of choice for peptic ulcer therapy. It is available in several brands in the Sudanese pharmaceutical market. The aim of this study was to evaluate the quality, safety and efficacy of the different brands and to assure the interchangeability among different brands and the originator (Zantac®). Four brands available in the market were assessed “evaluated” using pharmacopoeial parameters for quality such as weight variation test, hardness test, friability test, dissolution test and assay along with the similarity\disimilarity factors were evaluated. The results obtained in this study showed that the different brands satisfied pharmacopoeial parameters, although not all of them were pharmaceutically equivalent or interchangeable with the originator.

Key words: Ranitidine, Sudanese drug market, quality control, interchangeable.

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INTRODUCTION

Pharmaceutical products play an important role in improving the health and promoting the well-being of every individual. Their quality is a source of great concern worldwide, particularly in many developing countries (1). Reports indicate that the availability of substandard and counterfeit (fake) drugs has reached a disturbing proportion in resource-poor settings (2). The United States Pharmacopeia (USP) defines substandard drugs as being 'genuine products that do not conform to the pharmacopoeial standards set for them (3). The most common reasons why drugs become substandard including poor manufacturing practices, the use of impure formulation ingredients, and the inadequate quality of active ingredients which can be caused by, among other things, decomposition due to high temperatures and humidity (4). There are also many instances when impure and toxic ingredients have been added to the manufacturing process rendering the medicines produced not only substandard but harmful (5). Crucially these are not detected in the drug regulatory process and the drugs pass through the system.

Counterfeit and substandard drugs reached high percentages of the total drugs supply in many developing countries, for example, 36% of samples from Nigeria and 40% of samples from Thailand contained quantities of active ingredients that were outside the pharmacopoeial limits. Six drugs had no active ingredient at all (6).

The safety and efficacy of drug products can be guaranteed when their quality is reliable and reproducible from batch to batch. To ensure the requisite quality, drug manufacturers are required to test their products during, after manufacturing and at various intervals during the shelf life of the product. The Use of poor quality drugs has serious health implications, these includes; Increased mortality and morbidity, Engendering of drug resistance and loss of medicine efficacy and Loss of confidence in health systems and health workers (7). According to the United States Food and Drug Administration (USFDA), during the last three decades the bioavailability and bioequivalence of drug products, and drug product selection have emerged as critical issues in pharmacy and medicine (8). Concern about lowering health care costs has resulted in a tremendous increase in the use of generic drug products; where currently the orders for drugs by generic products represented by about more than one-half of all written prescriptions(9). Some publications have shown that consumers felt that a generic medicine did not work either as effectively, or at all, in comparison to when they were taking the originator medicine (10).

Ranitidine belongs to a class of drugs known as H₂-blockers, which blocks the action of histamine on stomach cells and hence reduces stomach acid production. It is used mainly for treatment of

gastric and duodenal ulcers, to treat uncomplicated gastrointestinal esophageal reflux disease (GERD) and to prevent the occurrence of stress ulcers (11).

MATERIALS AND METHODS

Materials

Four brands from ranitidine hydrochloride 150 mg were selected from different geographical regions; these products were the originator Zantac(Glaxo); others include one from Asian country (UAE), one from Egypt and the forth one from local Sudanese manufacturer (table 1). Samples were obtained from the retail outlets from private pharmacies and drug stores in Khartoum. The drug samples were purchased in their original package as supplied by the manufacturers and protected from direct sunlight.

Table 1: General information for different brands involved in the study

Brand Name	Zantac*	Ranitidine	Ranacid	Rantag
Sample Code	A	B	C	D
Batch Number	5R5E	141006	236	130
Mfg. date	May\2014	Mar\2014	Apr\2015	Apr\2014
Exp. Date	May\2017	Mar\2017	Apr\2017	Apr\2017
Country of origin	Spain	Egypt	Sudan	U.A.E.
Package style	Blister	Blister	Strip	Strip
Price\tablet(USD)*	0.28	0.11	0.03	0.18

A* is the reference product
USD* United States Dollar

Methods

Assay:

Ten tablets were transferred into volumetric flask of 250 mL, shaken with suitable volume of the mobile phase until the tablets had been disintegrated completely, and then filtered after volume completion; the filtrate was stepwise diluted, to obtain a concentration of ranitidine similar to that of the Standard preparation concentration ($1500/250 \times 2/10 \times 2/250$).

Separately equal volumes (about 10 μ L) of the standard preparation and the assay preparation were injected into HPLC system (Agilent®126 Infinity), then the chromatograms were recorded, and area responses for the major peaks were measured (12).

Weight variation:

Variation in weight was checked on Mettler® AE 240 sensitive balance. 10 tablets of each brand were selected randomly. The percentage weight variation from average tablet weight was calculated according to USP specification, (13) as per following formula:

$$X_i = w_i \times A \setminus \hat{W}$$

Where,

X_i = individual estimated content of the unit

w_i = individual weight of the unit

A = content of drug substance (% of label claim)

\hat{W} = mean of individual

Hardness:

This test was conducted on 10 tablets of each brand. Hardness of all brands was checked on Hardness Tester of Erweka® TBH 125. The hardness value of each tablet was evaluated and average value was calculated and compared.

Friability:

Friability test has been performed on 10 tablets of each brand of ranitidine by subjecting to a uniform tumbling motion for specified period of time i.e. 25 of rotations/minute for 4 minutes in Friability tester (Fine Scientific Instrument®) and the weight loss was determined according to USP specification (14).

Dissolution:

The test was conducted on DST-600 Fine Scientific Instruments® dissolution tester. It was performed with the paddle apparatus I in 900 ml 0.1 N HCL dissolution media at 50 rpm for 5,10,15,20,30,45 and 60 minutes. Tablets were placed in the vessels at the beginning of each test and the stopwatch was started simultaneously. In order to minimize evaporation vessels are covered during the run with plastic covers. Samples were removed using 10 ml volumetric pipette, and then filtered, the absorbance measured using UV-Spectrophotometer S-1100 Scinco®.

Similarity Factor:

The similarity factor (f_2) is a logarithmic reciprocal square-root transformation of the sum of squared error and is a measurement of the similarity in the percent dissolution between the two curves. The following equations were used to calculate difference factor f_1 and similarity factor f_2 :

$$F_1 = [(\sum_{t=1}^n |R_t - T_t|) / \{\sum_{t=1}^n R_t\}] \times 100$$

$$F_2 = 50 \cdot \log \{ [1 + (1/n) \sum_{t=1}^n (R_t - T_t)^2]^{-0.5} \} \cdot 100$$

Where n is the number of time points, R_t is the dissolution value of reference product at time t , and T_t is the dissolution value for the test product at time t (15).

Price variation study:

The per unit retail price of the different brands of ranitidine under study was recorded and compared.

Data Analysis

The uniformity of mass, hardness, friability and assay tests were analyzed with simple statistics

using Microsoft Excel Program while the dissolution profiles were analyzed by difference factor (f1), similarity factor (f2).

RESULTS AND DISCUSSION

Table 2: Uniformity of Mass test results

Brand Name	Zantac*	Ranitidine	Ranacid	Rantag
Mean	0.306 (+2.3/-2.9)	0.407 (+1.5/-1.0)	0.257 (+3.9/-2.3)	0.296 (+3.7/-2.0)
Min.*	0.297	0.403	0.251	0.290
Max.*	0.313	0.413	0.267	0.307
SD*	0.004	0.003	0.005	0.004
RSD%*	1.3	0.74	1.95	1.35

Min.*: Minimum weight

Max.*: Maximum weight

SD*: Standard deviation

RSD*: Relative standard deviation

Weight*: In Gram

Table 3: Hardness test results

Sample Code	A*	B	C	D
Average	16.03	18.90	9.81	11.26
SD*	1.22	1.65	1.27	0.35
RSD%*	7.63	8.73	12.92	3.11

Hardness*: In Kilopond (kp)

Table 4: weight loss percent (Friability test)

Sample Code	A*	B	C	D
Loss Percent	0.03	0.01	0.00	0.00

Table 5: comparison of F1 and F2

Comparison Products	F1 value	F2 value
A Vs B	3	76
A Vs C	9	47
A Vs D	9	47
B Vs C	9	49
B Vs D	9	49
C Vs D	2	81

Table 6: Percent content (Assay):

Sample Code	A*	B	C	D
Initial time	100.0	98.9	99.9	99.7

Error bar used: standard error (SE) taking A as reference

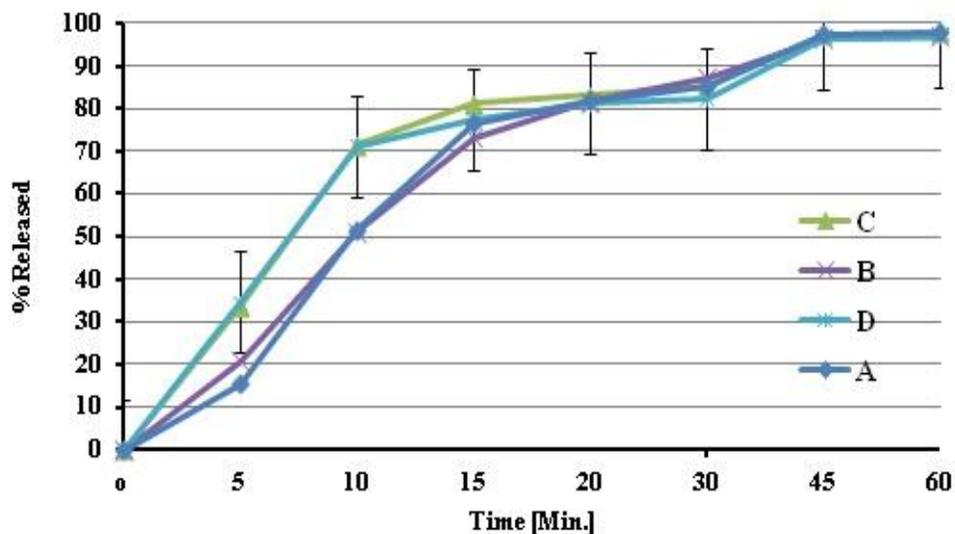


Figure 1: Dissolution profiles of different brands of ranitidine

Uniformity of dosage units (weight variation):

Table 2 showed the data of the uniformity of dosage unit test for A, B, C and D respectively; according to the product label, all of them contain 0.150 gram from ranitidine hydrochloride active material but they were of different total weights probably because of different excipients used for the manufacturing which increase the bulk or weight of the tablet, and also different punch sizes used for compressing tablets. All samples complied with the pharmacopoeial specification i.e. that the acceptance value of the first 10 dosage unit is less than L1 ($\pm 15\%$).

Hardness test:

Referring to table 3; the values of hardness for all brands were met with the requirements. Results showed that brand B has the highest value of force to break (18.90kp) while the local brand C has the lowest value (9.81kp), comparing these values with average means of their weights (table 2), showed that brand B with highest average weight (0.407) needed more force to break and brand C with lowest average weight (0.257) needed lowest force to break.

Friability test:

All samples in this study complied with USP-specification; that was no loss in their initial weight by more than 1.0% (table 4). Since ranitidine tablets were film-coated to resist humidity, this would justify the minor changes in samples initial weights and the high mechanical strength may be due to the film coating.

F1&F2 values:

According to table 5, brand B was the only brand that was very similar to the reference product with highest F2 value (76) and lowest F1 value (3) among the other three different brands, other

brands (C&D) including the locally manufactured have F2 value near to 50 (47) and little more high F1 value (9) but less than 15, showing that they were nearly similar to the reference product A, but not pharmaceutically equivalent. When compared the three generic product with each other taking product B as reference (table 5), they showed that products D and C were more similar to B than the reference product (more F2 value), with similar F2 (49), and the comparison of these products with each other; D Vs C showed that they were very similar to each other with F2 value more than 80 and F1 value less than 3.

Assay test:

As indicated in table 6, all brands of ranitidine tablets complied as per the USP specification. The highest percentage content was obtained for the reference brand “A” (100.00 %), while the least drug content was obtained for “B” brand (98.9%).

Rate of release:

The USP specifies that the amount of ranitidine released should not be less than 80% of the labeled amount at 45 minutes. According to figure 1, all brands released amount of the drug within USP specification at the 20th minute and these continued till 30th minute in which the rate of release started to increase and reached more than 90% in 45th minute. From 45th minute up to 60th minute all brands continued at constant rate near 100%.

During the first 5th minute, brand A (the reference product) and B (the similar product) showed rate of release less than 20%, while the local brand C and the other imported brand D showed more than 30% rate of release. These patterns continued till the 15th minute in which all brands showed nearly similar rate of release. The reasons for that may be due to many factors such as properties of excipients used in the formulation, coating materials and manufacturing process; according to the results of hardness test (table 3), brand A&B observed to have highest breaking force values (16.03&18.90) than brands C&D, (9.81&11.26) respectively, As reported earlier this can also contribute to the cause for the observed slow drug release rate from those products. The inverse correlation between the hardness of the tablet and dissolution rate is due to the fact that the density of the tablet increased with increasing hardness and at the same time, the porosity decreased so that the dissolution medium could not penetrate the tablets and ultimately there is less dissolution of drugs (16).

Comparison regarding the price:

During the time of this, Sudan medicines market faces obstacles in the availability of medicines and hard currency, and this lead to big variation in the retail prices of medicines from the registered prices. According to table 1, there was noticeable variation in the price of products; the

reference product has the highest price among other products(0.28 USD/tablet) and almost ten times than the price of the locally manufactured product(0.03 USD/tablet) while the physiochemical properties of the locally manufactured brand did not differ markedly from the reference product; according to figure 1, the local brand started the release with percentage higher than the reference product and this make its medical effect in relief more fast. If we compare the price unit of D with B, the former has higher price while the later is more similar than it to the reference product.

CONCLUSION AND RECOMMENDATION

- These results indicate that it is important to assess the quality parameters of generic drugs not only after production but also when these are already being marketed.
- Results lead to the conclusion that not all analyzed drugs can be considered equivalent and interchangeable with its reference pharmaceutical drug (only one product). Although all generic drugs are in conformity with the pharmacopoeial tests performed, they have dissolution profiles different from that of the reference product.
- Pharmacopoeial tests can assure the safety of pharmaceutical product but not the equivalency, the similarity or interchangeability of generic drug with the reference product.
- The general believe of Sudanese people regarding the difference in quality between imported and locally manufactured medicines can be true to some extent, but the difference in price does not support that believe.

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