Journal of Pharmaceutical, Chemical and Biological Sciences
ISSN: 2348-7658
UGC Approved Journal
CODEN: JPCBBG
Impact Factor (GIF): 0.701
Impact Factor (SJIF): 3.905
December 2017- February 2018; 5(4):345-353
Published on: January 19, 2018

Research Article

Quality Assessment of Different Brands of Rabeprazole Tablets Marketed In Some Nigerian Cities

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Received: 09 November 2017 **Revised:** 16 December 2017 **Accepted:** 26 December 2017

ABSTRACT

An ultraviolet (UV) spectrophotometric determination of rabeprazole sodium content present in five tablet brands of the drug products available in Nigerian market was conducted to access the pharmacopoeial quality and compliance of these commercial brands. The study also evaluated some physico-chemical properties (crushing strength, weight variation, friability, disintegration and dissolution profiles) of the five commonly available formulations of rabeprazole (encoded as RPB-1, RPB-2, RPB-3, RPB-4 and RPB-5) sold in Nigeria. RPB-1 was the innovator brand. All the brands met the standard specifications when tested for weight variation, friability and disintegration. The comparison of percentage drug release of these tablets based on dissolution study demonstrated that RPB-3 (89%) complied best while RPB-5 (22%) did not comply with standard specification for drug release profile. Only two brands, RPB-1 and RPB-5 met the USP (85-115%) specification for the total active drug content, while their dissolution profile showed a consistent increase in the release of active ingredient in all the brands, except RPB-5 which displayed some erratic drug release pattern and failed to release its drug content maximally. Comparatively, the innovator brand, despite complying with the label claim for active content, took longer time to attain T_{50} and T_{80}. It also failed to attain T_{90} after 1h. The results of this study, however, showed that RPB-2, RPB-3 and RPB-4 could be considered bioequivalent and interchangeable with the innovator brand, and may be prescribed one in place of the other, while RPB-5 should be withdrawn from circulation by regulating authorities pending its proper certification and compliance.

Keyword: Quality Assessment; innovator brand; Rabeprazole; tablets; Nigeria; UV

INTRODUCTION

Generally, pharmaceutical dosage forms, such as tablets, with same drug content may not give the same therapeutic response as the differences of formulation additives in the tablets, physical form of the drug and variation in manufacturing process might give rise to variation in the observed dissolution profile and therapeutic effect in brands from different manufacturing companies. The dissolution of the drug from the tablet matrix depends on many factors, which include not only the physiochemical properties of drug but also the nature of formulation and the process of manufacturing [1-3]. The need for routine assessment of dosage forms in

circulation cannot be overemphasized, especially for highly patronized and expensive drug products that are marketed under various generic brands in many developing countries that are deficient in requisite infrastructure and logistics for standard drug distribution, storage and dispensing.

Rabeprazole sodium belongs to a class of anti-secretory compounds and is a substituted benzimidazole that inhibits gastric acid secretion [4]. It is chemically known as 2-[[[4-(3methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1H–benzimidazole sodium salt [5]. Rabeprazole works by inhibiting the action of the proton pumps which reduce the production of stomach acid. It is a partially reversible inhibitor of hydrogen/potassium adenosine triphosphatase (H+/K+ ATPase) which is activated in the acidic lumen of gastric parietal cells [6]. Rabeprazole is a relatively new proton pump inhibitor (PPI) used in the treatment of acid-peptic-related disorders (gastro-esophageal reflux disease [GERD], duodenal ulcer, gastric ulcer, gastric acid hypersecretory syndromes) and *Helicobacter* pylori [7].

Rabeprazole sodium is rapidly degraded in acid media, and thus, PPI formulations are usually stabilized in mixtures with alkaline reacting compounds. The exposure of Rabeprazole sodium to the acidic content of the stomach would lead to significant degradation of the drug and hence, reduced bioavailability [8]. The aim of the present investigation was to evaluate some physico-chemical properties (crushing strength, weight variation, friability, drug content, disintegration and dissolution profiles) of commonly available formulations of enteric-coated rabeprazole sodium tablets marketed in major Nigerian cities, with a view to determining the level of compliance of these brands with pharmacopoeial standards.

MATERIALS AND METHODS.

Sample Procurement and Assessment

a) **Samples:** The respective brands of rabeprazole sodium tablets (encoded as RPB-1, RPB-2, RPB-3, RPB-4 & RPB-5) used for this study were procured from various pharmacy premises in some Nigerian cities located at the southwest and south-south regions of the country. Information about the various brands such as brand name, producer's name, country of manufacture, manufacturing/expiry dates, batch/or lot number, label claim of potency of the drug and product registration status with the National Agency for Food and Drug Administration and Control (NAFDAC) were assessed. The tablets were also physically examined for shape, color, packaging and overall dosage form conformity.

b) **Reference Drug:** Standard rabeprazole sodium was procured from Shanghai Research Institute of Chemical Industry Testing Centre, China.

METHODS

Preparation of simulated intestinal fluid (phosphate buffer), pH 7.2

This was prepared as follows: A 34 g quantity of potassium dihydrogen phosphate was dissolved in 500 ml of distilled water. The pH was adjusted to 7.2 using 0.1 N NaOH and the volume was made up to 1000 ml with distilled water [9].

Preparation of simulated gastric fluid (SGF), pH 1.2 (without enzyme)

A 12.0 g quantity of sodium chloride was dissolved in about 5.3 L of distilled water and the pH adjusted to 1.2 using 0.1 N concentrated hydrochloric acid. The volume was made up to 6.0 L [9].

Weight Variation

Twenty (20) tablets were selected randomly and weighed individually. The average weight was calculated and individual weight was compared to the average weight. The tablet batches pass the test if not more than two of the individual weights deviate from the average weight by more than ± 7.5% and none deviated by twice ± 7.5% [10].

Crushing strength

Ten tablets were randomly selected from each brand of rabeprazole sodium. The tablet crushing strength was determined using Monsanto tablet hardness tester (Monsanto, India) [10].

Friability test

The percentage friability of the tablets from each brand was determined using Erweka® friabilator. It should be less than 1%. Ten tablets

taken from each brand were selected randomly and weighed, then placed in the friability test apparatus and rotated about 100 times. The tablets were then carefully dusted and reweighed to ascertain weight loss [10].

Disintegration Test:

The disintegration test was performed according to pharmacopoeial procedure. Six tablets from each formulation were weighed and placed in the baskets. The apparatus was operated using SGF, pH 1.2 as immersion fluid at 37± 1°C for 2 h. The tablets were observed for any sign of disintegration, cracking or softening. The tablets were then removed and the immersion fluid replaced with SIF (phosphate buffer; pH 7.2). The apparatus was operated on same condition as SGF for 1h. The specification for the disintegration of enteric coated tablet in phosphate buffer (pH 7.2) is 1 h according to British Pharmacopoeia [10].

Dissolution Test

Drug release studies were carried out using an Erweka® dissolution test apparatus set at 100 rpm for 1 h in simulated gastric fluid (pH 1.2), and after that, for 1h in intestinal fluid (phosphate buffer, pH 7.2) as dissolution medium at 37°C ± 1°C. After an interval of 10, 20, 30, 40, 50 and 60 min respectively, 10 ml of the samples were taken out and 10 ml of fresh phosphate buffer pH 7.2 added to keep the volume of dissolution medium constant. The sample was analyzed using UV spectrophotometer at 207 nm for simulated gastric fluid and 230 nm for simulated intestinal fluid and the percent drug release was calculated [10].

Content of active ingredient

Ten tablets from each brand of rabeprazole sodium were crushed to powder in a mortar. A 10-mg equivalent of rabeprazole was weighed, transferred into a volumetric flask and dissolved in 100 ml of phosphate buffer. The solution was filtered through a Whatman® filter paper. A 2 ml volume of the filtrate was withdrawn and diluted to 10 ml. The absorbance of the resulting solution was measured at the 230 nm against a solvent blank using a Jenway® UV/Vis Spectrophotometer (Model 6405). The mean percentage drug content was determined for each brand [10].

Bioequivalence Determination using Dissolution profile.

Difference Factor (f_1) and Similarity Factor (f_2) were calculated to compare the dissolution efficiency of the various brands. F1 is the percentage difference between two curves at each point and is a measurement of the relative error between the two curves while 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 f_1 and f_2.

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} X100$$

$$f_2 = 50 \log \left\{ \left(1 + \frac{1}{n} \sum_{i=1}^{n} (R_t - T_t)^2 \right)^{-0.5} X100 \right\}$$

Where

n = number of time points,

R_t =dissolution value of reference product at time t and

T_t =dissolution value for the test product at time t.

Similarity factor has been adopted by [11], the European Agency for the Evaluation of Medicinal Products [12] and the Committee for Proprietary Medicinal Products (CPMP) to compare dissolution profiles. Two dissolution profiles are considered similar and bioequivalent, if f_1 value is between 0 and 15 while f_2 value is between 50 and 100 [11].

RESULTS AND DISCUSSION

The results of the physical examination of the respective brands of rabeprazole tablets used for this study are presented in Table 1, showing label claim, batch number, date of manufacture and expiration, manufacturer, country of manufacture and registration status with the National Agency for Food and Drug Administration and Control, NAFDAC in Nigeria. All the brands of rabeprazole tablets studied were registered with NAFDAC except RPB-5 which bears no registration number. The Nigerian drug statutes stipulate that any drug product in the country that is not registered with NAFDAC is fake.

The standardization procedure (Figs. 1, 2) for rabeprazole in phosphate buffer (pH 7.2) and simulated gastric fluid (without enzyme; pH 1.2) yielded equations 2 & 3 respectively:

$y = 0.0567x - 0.002$ $(R2 = 0.9955)$……(2)

$y = 12.73x + 0.0036$ $(R2 = 0.9967)$……. (3)

Table 1: Product information for various brands of rabeprazole sodium tablets studied:

Tablet Brand	Date of manufacture	Expiry Date	NAFDAC Registration status	Label drug content (mg)
RPB-1	10/2015	09/2017	Registered	20.00
RPB-2	10/2015	09/2017	Registered	20.00
RPB-3	06/2015	05/2017	Registered	20.00
RPB-4	01/2015	01/2017	Registered	20.00
RPB-5	Not shown	02/2018	Not Registered	20.00

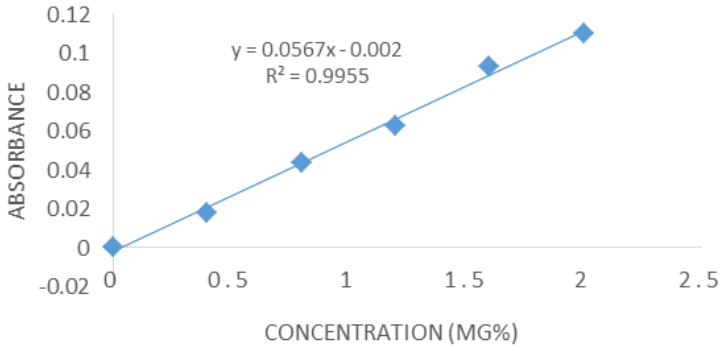

Fig. 1: Calibration curve of Rabeprazole in phosphate buffer solution, pH 7.2 at 230nm

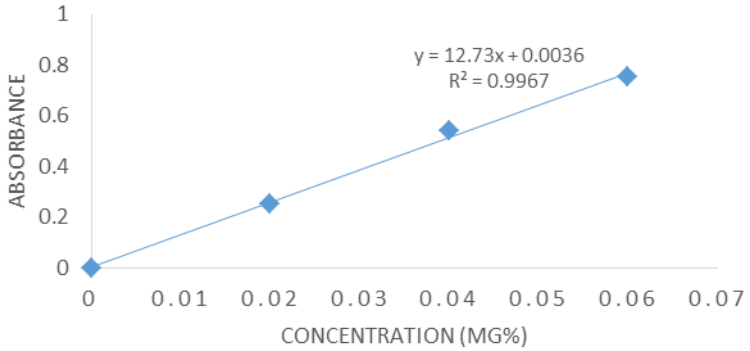

Fig. 2: Calibration curve of Rabeprazole in SGF, pH 1.2 at 207nm

The USP specified that the amount of active ingredient should fall within 85-115%. Table 3 showed the results of actual and total percentage drug content for the respective

brands of rabeprazole sodium tablet studied as against the label claim of 20 mg. Only RPB-1 and RPB-5 met the specification for total drug content, though. Table 4 showed the data on the tablet uniformity of weight. The United States Pharmacopoeia [9] specified that for tablets or capsules that weigh between 130-324 mg, standard deviation of weight should not exceed 7.5% and for tablet or capsules that weigh more than 325mg, standard deviation of weight should not exceed 5%. The various brands thus passed the test for uniformity of weight. The enteric-coated dosage forms are intended to resist the release of their active ingredients in the acidic gastric fluid but to disintegrate and release their contents in the less acidic environment of the intestine. The USP recognizes the use of enteric-coated dosage forms in situations where it may irritate the gastric mucosa. Table 5 shows the results of crushing strength, friability and disintegration time test for the respective brands of rabeprazole tablets. The USP recommends a crushing strength of 4-8 kgf for uncoated tablets. However, the brands of product under consideration are entirely enteric-coated and are expected to be of higher crushing strength. The crushing strength recorded ranged from 6.90±0.51 - 14.82±1.52 kgf, with RPB-3 showing the least value of 6.90±0.51 kgf. The tablets were all enteric-coated, hence were not expected to fragment easily on experiencing mechanical shock.

Table 2: Physical assessment of the various brands of Rabeprazole sodium tablets studied

Brand name	Color	Shape	Packaging	Dosage form
RPB-1	Yellow	Round	Aluminum foil blister	Enteric coated tablet
RPB-2	Yellow	Round	Aluminum foil blister	Enteric coated tablet
RPB-3	Yellow	Round	Aluminum foil blister	Enteric coated tablet
RPB-4	Yellow	Round	Aluminum foil blister	Enteric coated tablet
RPB-5	Yellow	Round	Aluminum foil blister	Enteric coated tablet

Table 3: Results of drug content for the respective brands of Rabeprazole sodium tablets

Brand name	Label content (mg)	Actual content (mg)	Actual content (%)
RPB-1	20.00	20.55	102.75
RPB-2	20.00	14.90	74.50
RPB-3	20.00	15.96	79.80
RPB-4	20.00	16.23	81.15
RPB-5	20.00	17.11	85.55

NB: The USP specified amount of active ingredient to fall within 85-115%

Table 4: Results of uniformity of tablet weight for the respective brands of Rabeprazole sodium

Brand name	Mean weight (mg)	Coefficient of variation (%)	Remarks
RPB-1	161.55±3.15	1.95	Passed
RPB-2	218.70±4.77	2.12	Passed
RPB-3	146.60±1.27	0.87	Passed
RPB-4	218.00±5.07	2.33	Passed
RPB-5	154.30±2.70	1.75	Passed

NB: The United States Pharmacopoeia (2012) specified that for tablets or capsules that weigh between 130mg-324mg, standard deviation of weight should not exceed 7.5% and for tablet or capsules that weigh more than 325mg, standard deviation of weight should not exceed 5%.

Table 5: Tablet Crushing strength, Friability and Disintegration time for the respective brands of Rabeprazole sodium studied

Brand name	Crushing strength (kgf)	Friability	Disintegration time (min.) (SIF, pH 7.2)	Disintegration time (min.) (SGF, pH 1.2)
RPB-1	12.30±2.61	0.00	24.01±2.91	**ND after 2hr
RPB-2	10.43±2.55	0.00	8.31±2.59	**ND after 2hr
RPB-3	6.90±0.51	0.00	16.48±6.45	**ND after 2hr
RPB-4	11.52±1.49	0.00	12.64±5.01	**ND after 2hr
RPB-5	14.82±1.56	0.00	27.42±9.29	**ND after 2hr

Note: **ND = No disintegration

Note: The International Pharmacopoeia, 2009, specifies that no delayed release enteric coated tablet should disintegrate in simulated gastric fluid less than 2hr, but should be able to disintegrate in phosphate buffer in less than 1hr.

The tablets of the various brands disintegrated in less than 30 min in simulated intestinal fluid (SIF, pH 7.2) at 37o C with the least value of 8.31±2.59 min recorded for RPB-2. None of the brands tested disintegrated in simulated gastric fluid (SGF) without enzyme (pH 1.2) at 37o C after 2 h. The International Pharmacopoeia [13] specifies that no delayed release enteric coated tablet should disintegrate in simulated gastric fluid in less than 2 h, but should be able to disintegrate in phosphate buffer in less than 1 h. According to the USP, enteric coated tablets are to show no evidence of disintegration after 1 hour in simulated gastric fluid.

Figures 3 and 4 represented the dissolution profile for the various brands of rabeprazole in SIF at 230 nm and in SGF at 207 nm respectively. In the SIF, there was a consistent increase in the release of active content for the period of the dissolution test for the respective brands of rabeprazole except the RPB-5 which displayed erratic drug release pattern and also failed to release maximally. Table 6 showed the T50 for the brands of rabeprazole tablets under study in SIF in this order: RPB-2<RPB-4<RPB-1<RPB-3. RPB-5 failed to attain T50 after 1 h. None of the brands attained T90 after 1hr. For drug release at T80 (Table 5), the outcome was as follows: RPB-4<RPB-2<RPB-1<RPB-3. RPB-5 also failed to attain T80. In SGF, the release of drugs for the entire brands studied was stunted as only less than 10% of the active drug could be released after 1 h. This dissolution pattern in SGF is not out of place since enteric-coated tablets are not designed to break down, nor release their active content in an acidic medium. According to the USP, the enteric-coated dosage forms are intended to resist the release of their active ingredients in the acidic gastric fluid but to disintegrate and release their contents in the less acidic environment of the intestine. In comparing the drug release pattern of the brands, the innovator brand (RPB-1), though gave the specified amount of active content, took longer time to attain T50 or T80 while failing to attain T90 after 1 h. Generally, the observed differences in drug release pattern of generic brands have been attributed to product formulation technology used by different manufacturers, which might also have to do with excipients used in the formulations [14-16].

Table 7 was the results of bioequivalence testing of different brands of rabeprazole sodium tablets via the determination of their similarity and difference factors. As the name implies, similarity factor (F_2) stresses on the comparison of closeness of two comparative formulations. The F_2 parameter is commonly used to establish similarity of two dissolution profiles. Dissimilarity factor focuses on the difference in percentage dissolved between reference product and test product at various time intervals. F_1 factor is used to calculate the approximate % error in drug release profile [17]. Hence, F_2 factor was used as a tool to compare the dissolution profiles and F_1 the difference factor.

Table 6: Time of attainment of T50, T80 or T90 for brands of Rabeprazole tablets in the SIF

Product	T50 (min)	T80 (min)	T90 (min)
RPB-1	22.00	39.00	NA
RPB-2	35.00	45.00	NA
RPB-3	7.50	38.00	NA
RPB-4	8.50	29.00	NA
RPB-5	NA	NA	NA

Note: NA = Not attained

Table 7: Results of bioequivalence test for the various brands of Rabeprazole sodium tablets

Product	F_1	F_2
RPB-1	Reference product	Reference product
RPB-2	6.194	61.686
RPB-3	4.798	66.673
RPB-4	1.788	72.405
RPB-5	81.122	8.936

Note: F_1 (Difference factor). The difference factor in range of 0-15 is acceptable.
F_2 (Similarity factor). The similarity factor in range of 50-100 is acceptable to US FDA.

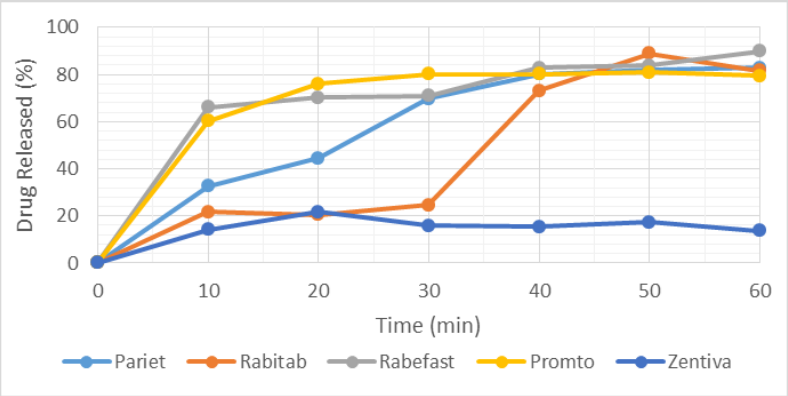

Fig. 3: Graph of dissolution profile for the various brands of Rabeprazole in phosphate buffer solution, pH 7.2 at 230nm.

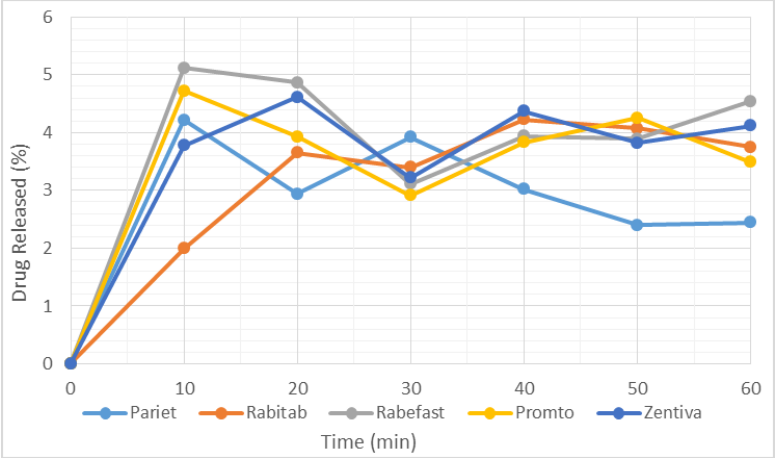

Fig. 4: Graph of dissolution profile for the various brands of rabeprazole in SGF, pH 1.2 at 207nm

From their respective F_1 and F_2 all the tested brands of rabeprazole (except RPB-5) could be said to be bioequivalent with the innovator brand as their F_1 and F_2 values were within the standard acceptable range (0 - 15 for F_1 and > 50 for F_2). The F_1 and F_2 values for RPB-5 were 81.22 and 8.936 respectively.

CONCLUSION

The results of this study indicated that the innovator drug (RPB-1) did not release its content quicker than the other brands tested. RPB-5, following the regulatory requirements for drugs in Nigeria could be described as fake as it was not registered with the drug regulatory agency (NAFDAC) in Nigeria where it is marketed. Its inability to release up to 50% of its claimed drug content after 1 h may provide further insight into its quality. It can be concluded that RPB-2, RPB-3 and RPB-4 were bioequivalent and interchangeable with the innovator brand RPB-1. The generic substitution of these bioequivalent brands would therefore engender improved patients' compliance and therapeutic efficiency, bearing in mind the high cost of the innovator brand in Nigeria.

CONFLICT OF INTERESTS

The authors declare no conflict of interest in the course of this study.

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Cite this article as:
Ukwueze SE, Ogbokor M, Ezealisiji KM . Quality Assessment of Different Brands of Rabeprazole Tablets Marketed In Some Nigerian Cities. J Pharm Chem Biol Sci 2017; 5(4):345-353.