



***In vitro* quality evaluation of brands of promethazine tablets marketed in Edo State, Nigeria**

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Abstract

The increasing number of multisource pharmaceuticals has necessitated the need for continuous quality assessment of products available for patients' consumption. Promethazine is an anti-histamine used in cases of nausea, vomiting, motion sickness etc. The study was to examine the *in vitro* quality parameters for ten brands of promethazine hydrochloride tablets sold in retail pharmacies in Edo State, Nigeria. The parameters determined were identification, weight variation, friability, hardness, disintegration, dissolution rate and assay. All samples were evaluated for conformity with British Pharmacopoeia (BP) 2017 standards. Results obtained showed tablet weight ranging from $0.08 \text{ g} \pm 1.77 \%$ to $0.255 \text{ g} \pm 3.557 \%$, hardness from 4.36 ± 0.58 to $8.33 \pm 3.21 \text{ kg/cm}^2$, friability of $< 1 \%$, disintegration time of 2.47 ± 0.90 to $69.66 \pm 7.23 \text{ min}$ and assay of 61.32 ± 2.04 to $183.19 \pm 0.11 \%$. The ten batches but one released more than 80 % of their drug content within 30 min. Analysis of similarity factor revealed other samples but PR-7 can be interchangeable with PR-1 based on dissolution profile. The results showed that not all samples examined passed all the pharmacopoeia tests for satisfactory quality. Thus, they all cannot be used interchangeably in clinical practice.

Keywords: Promethazine; Quality Control; Dissolution; Pharmacopoeial specifications

INTRODUCTION

The pharmaceutical sector is faced with a large number of multisource pharmaceutical products for public consumption and this could be due to affordability and accessibility. Consequently, some counterfeit products crept in along with other genuine drugs. The deleterious implications of counterfeit drugs are understood to be a central challenge to the integrity of public health systems around the globe, as well as a direct threat to individual health and welfare. The prevalence of counterfeit drugs appears to be rising and has not been countered by close cooperation

between pharmaceutical companies, government, and international organizations concerned with trade, health, customs and excise, and counterfeiting. The issue of drug counterfeiting has been reported widely even in newsprints and other media outfits [1]. The World Health Organization (WHO) defines counterfeit drugs as "drugs that have been deliberately or fraudulently mislabeled with respect to identity and/or source" [2].

The major factors contributing to the prevalence of counterfeit drugs in Nigeria include ineffective enforcement of existing laws, non-professionals in drug business, loose

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control systems, high cost of genuine drugs, greed, ignorance, corruption, illegal drug importation, chaotic drug distribution network, demand exceeding supply among many others [3].

Pharmaceutical equivalence studies of medications are carried out to determine if pharmaceuticals meet up to requirements of standards as prescribed in the official compendia. Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration. [4]. Pharmaceutically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same compendial or other applicable standards (i.e. strength, quality, purity, and identity), but they may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time and within certain limits labeling [4]. Pharmaceutical equivalents are the same drug entity, the same type of dosage form, the same dose and meet the same compendial requirements.

The increase in demand for pharmaceutical products results in the production of different categories of these products, and also diversity in brands. It has therefore become a necessity to keep the quality of pharmaceutical products in constant check, especially those that have already found their way to the market for patients' use. Comparative analysis of the different available brands to the official standard would be an effective measure to ascertain the quality of these products, ensuring that they meet required specifications with a view to detecting sub-standard products.

Promethazine is a first-generation antihistamine, used to treat allergies, insomnia and nausea. It may help with some symptoms associated with the common cold. It may also

be used for sedating people who are agitated or anxious [5]. Promethazine is available as hydrochloride and teoclate salt. Promethazine teoclate has a longer duration of action than the hydrochloride.

It is a phenothiazine derivative structurally different from the neuroleptic phenothiazines with similar but different effects. It acts primarily as a strong antagonist of the H1 receptor (antihistamine) and a moderate muscarinic acetylcholine (mACh) receptor antagonist (anticholinergic) [6] and also has weak to moderate affinity for the 5-HT_{2A} [7], dopamine-2 [8,9], and α 1-adrenergic receptors, where it acts as an antagonist at all sites. It has also found a notable use as a local anesthetic, by blockade of sodium channels [10].

Promethazine has a chemical name, N, N-dimethyl-1-phenothiazin-10-ylpropan-2-amine with chemical formula C₁₇H₂₀N₂S and molar mass 284.42 g/mol. Solid promethazine hydrochloride is a white to faint yellow, practically odourless, crystalline powder. Slow oxidation may occur upon prolonged exposure to air, usually causing blue discoloration. Its hydrochloride salt is freely soluble in water and somewhat soluble in alcohol. Promethazine is a chiral compound, occurring as a mixture of enantiomers.

Promethazine has a variety of medical uses, including sedation, nausea and vomiting association with anesthesia or chemotherapy. It is commonly used postoperatively as an anti-emetic. The anti-emetic activity increases with increased dosing; however, side effects also increase, which often limits maximal dosing. For moderate to severe morning sickness and hyperemesis gravidarum, promethazine is drug of first choice in the UK ahead of metoclopramide or prochlorperazine, being preferred as an older drug with which there is a greater experience of use in pregnancy [11,12]. It also finds usefulness for allergies such as hay fever and together with other medications in anaphylaxis, to aid with

symptoms of the common cold, motion sickness, hemolytic disease of the newborn, anxiety before surgery [13].

Several studies have been reported for the methods used in determination of promethazine in bulk, formulations as well as in body fluids. These include: spectrophotometry [14, 15], HPLC [16, 17].

The objective of this study was to assess the quality of different brands of promethazine tablets commercially found in Edo State of Nigeria, using compendia procedures found in the British Pharmacopoeia.

EXPERIMENTAL METHODS

Drugs and chemicals. Promethazine hydrochloride powder was purchased from AK Scientific, California. Ten brands of promethazine tablets were purchased from retail pharmacy shops in Edo State. The samples were properly checked for their NAFDAC registration numbers, batch numbers, production and expiry dates. They were randomly designated as PR-1, PR-2 to PR-10. All other chemicals were of analytical grade and include: Hydrochloric Acid (JHD, China), Petroleum ether (JHD, China), Anhydrous sodium sulfate (Guangdong, China), Sulfuric acid (JHD, China), Sodium hydroxide (Loba, India) and Distilled water.

Instruments. Instruments used in the study were weighing balance (Mettler Toledo), Hardness Tester (Mosanto, UK), Friability test apparatus (Campbell FTA-20 Single drum), Disintegration Test Apparatus (Esico International, India), Dissolution test apparatus (Erweka DT600), M530 FTIR Spectrophotometer (Buck Scientific) and UV-visible spectrophotometer (Cecil CE 2000 series).

Determination of uniformity of weight.

Twenty tablets from each of the brands were weighed individually with an analytical weighing balance. The average weights for

each brand as well as the percentage deviation from the mean value were obtained.

Identification test for promethazine tablet using sulfuric acid.

Promethazine hydrochloride tablet was identified in accordance to BP [18] as follows; ten tablets were picked randomly from each brand and powdered using a porcelain mortar and pestle. A quantity of powdered tablet containing 40 mg was weighed respectively and transferred into a test tube, 5 mL of sulfuric acid was added, the mixture was allowed to stand for 5 minutes to observe a red colouration.

Identification test for promethazine hydrochloride tablet using Infrared Spectroscopy.

A quantity of the powdered tablet equivalent to 40 mg of promethazine hydrochloride in each case was weighed into a 100 mL beaker, 10 mL of distilled water and 2 mL of 1M sodium hydroxide solution were added, it was extracted with 15 mL ether using a separating funnel. The ether layer was washed with 5 mL water dried with anhydrous sodium sulfate and evaporated to dryness. The infrared spectrum of each sample was determined.

Fourier-Transform Infrared Spectroscopy (FTIR).

FTIR spectra were obtained by using an FTIR spectrophotometer. The samples were mixed thoroughly with potassium bromide (KBr) in a Sample to KBr ratio of about 1:5 respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Scans were obtained at a resolution of 4 cm^{-1} , from $4,000$ to 300 cm^{-1} .

Hardness test. The tablet hardness tester was used to determine the crushing strength of the tablets. Five tablets were randomly selected from each brand and the pressure at which each tablet crushed was recorded.

Friability test. Twenty tablets from each sample were taken and weighed then placed on the friabilator, which was then operated at 25

rpm for 4 minutes. The tablets were dedusted, reweighed and the difference in tablet weight was determined and percentage friability was calculated as follows [19]:

$$\text{Friability} = \frac{W_1 - W_2}{W_1} \times 100\%$$

Where, W_1 = initial weight and, W_2 = final weight

Disintegration test. Six tablets were randomly selected from each sample and respectively placed in the six basket units of Esico disintegration apparatus, containing distilled water, maintained at a temperature of 37 °C. The time taken for all the tablet particles in each unit to pass through the mesh was recorded.

Preparation of calibration curve. For the standard promethazine powder, 0.1g of sample was weighed and transferred into a 100 mL standard flask (wrapped with foil) containing distilled water and shaken vigorously, it was made up to volume thereby containing 1000 µg/mL of the standard promethazine. From the stock solution, 10 mL was measured and transferred to 100 mL standard flask whereby the volume was adjusted with distilled water making it containing 100 µg/mL. Serial dilutions were further carried out to obtain concentrations between 10 – 100 µg/mL and the absorbance of each of the solution was measure at 249 nm. A plot of absorbance versus concentration of promethazine was made from which the regression equation was calculated.

Dissolution test. The dissolution rate test was carried out using the USP apparatus 1 (basket method) in 6 replicates of each brand. The dissolution medium was 900 mL of 0.1 N HCl which was maintained at 37.0 ± 0.5 °C. In all the experiments, 5 ml of dissolution sample was withdrawn at 0, 10, 15, 30, 45 and 60 min and replaced with equal volume to maintain sink condition. Samples were filtered and assayed by UV-VIS spectrophotometer at 249 nm. The concentration of each sample was determined from a calibration curve obtained

from standard samples of promethazine. The percent dissolutions were computed.

Analysis of similarity factor. Similarity factor (f_2) has been adopted by the United States Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products to compare dissolution profiles [20,21]. The dissolution profiles were analyzed by a mathematical model, similarity factor (f_2). Mean dissolution values were employed to estimate the similarity factor (f_2). A factor value of 50 or greater (50-100) ensures sameness or equivalence of the two products. The equation below was used to calculate similarity factor (f_2):

$$f_2 = 50 \cdot \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \cdot 100 \right\}$$

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.

Assay of promethazine hydrochloride tablet. The procedure was carried out protected from light and the BP 2017 promethazine hydrochloride tablet monograph was employed as follows: a quantity equivalent to 50 mg of pulverized promethazine hydrochloride tablet was weighed and dissolved in 10 mL of 2 M hydrochloric acid and 200 mL of distilled water was added, it was shaken for 15 minutes and sufficient amount of distilled water was added to make up to 500 mL, 50 ml of the mixture was obtained, shaken and allowed to settle, then 5mL of supernatant liquid was transferred to a flask containing 10 mL of 0.1M hydrochloric acid and thus made up-to 100 mL with water. The absorbance of the resulting solution was measured at a wavelength of 249 nm using UV spectrophotometer. Determination of promethazine hydrochloride was carried out in triplicate for each brand of tablet using the calibration curve conducted with the standard promethazine.

RESULTS AND DISCUSSION

Description of sample tablets. The tablet samples were checked to observe their shape, colour, scoring, coating with each given designated code name PR-1 to PR-10. All samples collected were within shelf life except for PR-2. All tablet colors were white except for PR-7 and PR-8 which are blue in colour. They all presented with a circular shape while PR-1, PR-2, PR-3 and PR-4 are the scored samples, PR-7 and PR-8 were the only sugar-coated brands employed in this study as shown in Table 1:

Weight variation test. All the samples except that of PR-5, PR-6, PR-7 and PR-8 passed the weight variation test with their percentage deviation from the mean less than 5 % specified in the British Pharmacopoeia [17] as illustrated in table 2. Weight variation is an important test for the evaluation of tablet because its variation lead to variation of content uniformity which ultimately results in sub-therapeutic dose or over dose of the tablet.

Identification test. All the samples except PR-7 and PR-8 gave the expected red colouration upon dissolution in sulfuric acid indicating the presence of promethazine in the tablet samples. The promethazine extracted from various tablet samples were identified by running their IR spectra and result represented as shown in figure 2. Overlaid FTIR spectra showed some similarities between the pure promethazine sample and other extracted brands of tablet. Characteristics bands were observed for tertiary amine stretch between $1050-1325\text{ cm}^{-1}$, C-N at about 1433 cm^{-1} with aromatic C-S and C-C stretchings at around $3076-3351\text{ cm}^{-1}$

and 1591 cm^{-1} respectively while aromatic amine also observed at 2370 cm^{-1} .

Friability testing. Friability testing result for the sample brands is as shown in Table 2. Thus, the brand most likely to lose particles during handling was brand PR-1, 0.198%, while the least likely to lose particles was brand PR-10, 2.439 %. Friability for all brands PR-9 and PR-10 were above 1% and can be said not to have complied with the compendial specifications. Friability testing was not conducted for PR-7 and PR-8 as they were coated tablets.

Hardness test. The hardness of a tablet is the crushing strength and it determines the ability of tablets to withstand the shock of handling without fracture or chipping and during transportation. It can also influence friability and disintegration of tablets. The harder a tablet, the less friable and the more time it takes to disintegrate. From table 2, brand PR-4 required the least pressure before fracture while brand PN-10 has the highest strength. A force of 4 kg/cm^2 is the minimum requirement for the hardness of a tablet [22]. Hence the tablets of all brands were satisfactory for hardness.

Disintegration test. Disintegration can be linked to drug dissolution and consequently bioavailability of a drug. The active ingredient incorporated in a tablet matrix is released rapidly as the tablet disintegrates; a crucial step for immediate release dosage forms because the rate of disintegration affects the dissolution and by extension the therapeutic efficacy of the medicine. All the uncoated brands complied with the compendial specifications for disintegration.

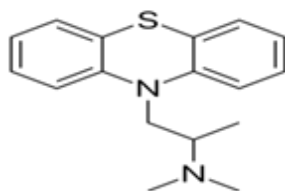


Figure 1: Structure of promethazine

Table 1: Information of ten different brands of promethazine tablets

Code	Manufacturer	Shape	Colour	Scoring	Coating	NAFDAC Reg. No.	Expiry Date	Batch No.
PR-1	Kesar Pharma (P) Ltd. India.	Circular	White	Scored	Uncoated	B4-7173	01/2021	T18069
PR-2	Marleyshree Pharmaceutical Co (Nig) Ltd. Kano, Nigeria.	Circular	White	Scored	Uncoated	A4-2542	05/2020	001
PR-3	New divine Favour Pharm. Ind. Ltd, Anambra State, Nigeria.	Circular	White	Scored	Uncoated	A11-0536	01/2023	NDF/OU T/0004
PR-4	Maxhael Pharma ltd. India.	Circular	White	Scored	Uncoated	B4-2798	03/2021	KM-002
PR-5	Surelife Pharma, Delta State, Nigeria.	Circular	White	Not scored	Uncoated	Nil	02/2021	055
PR-6	Rock Pharmaceutical Laboratories (PVT) Ltd. Pakistan.	Circular	White	Not scored	Uncoated	B4-0068	12/2021	59461
PR-7	Medico Remedies Ltd. 8&9 Dewen & Sons udyong Negar, India.	Circular	Blue	Not scored	Uncoated	A4-6472	09/2021	FEI801
PR-8	Vardhman Exports, Mumbai-400086.	Circular	Blue	Not scored	Sugar coated	A4-9929	01/2022	T21702
PR-9	Zhejiang DND Pharmaceutical Co. Ltd, China.	Circular	White	Not scored	Sugar coated	A4-0207	12/2020	180102
PR-10	Zhejiang DND Pharmaceutical Co. Ltd, China.	Circular	White	Not scored	Uncoated	B4-3499	05/2021	180601

NAFDAC -National Agency for Food and Drug Administration and control; Reg- Registration

Table 2: A summary of the quality control test undertaken on the brands of promethazine.

Sample code	Mean weight (g)	%Deviation from mean weight	Average Hardness Test \pm SD (kg/cm ²)	Friability (%)	Disintegration Time \pm SD (min)	Assay \pm SD (%) [n=3]
PR-1	0.255	\pm 3.557	4.67 \pm 1.15	0.198	6.66 \pm 2.29	103.05 \pm 0.05
PR-2	0.225	\pm 3.736	7.33 \pm 0.58	0.201	6.61 \pm 1.77	99.39 \pm 1.03
PR-3	0.236	\pm 4.133	5.85 \pm 1.44	0.197	2.47 \pm 0.90	97.10 \pm 0.04
PR-4	0.267	\pm 2.795	4.36 \pm 0.58	0.391	2.62 \pm 1.00	101.31 \pm 0.71
PR-5	0.198	\pm 5.338	8.33 \pm 3.21	0.417	13.84 \pm 1.10	94.19 \pm 1.02
PR-6	0.255	\pm 7.739	7.5 \pm 3.5	0.386	14.81 \pm 2.23	61.32 \pm 2.04
*PR-7	0.101	\pm 5.246	7.33 \pm 3.88	N/A	69.66 \pm 7.23	101.31 \pm 0.05
*PR-8	0.120	\pm 5.483	5.83 \pm 0.76	N/A	60.58 \pm 3.40	101.98 \pm 0.17
PR-9	0.08	\pm 1.77	8.50 \pm 0.50	1.204	8.99 \pm 0.68	128.54 \pm 0.39
PR-10	0.083	\pm 3.970	9.67 \pm 1.53	2.439	5.82 \pm 0.27	183.19 \pm 0.11

Calibration curve equation: $y = 0.0426x + 0.1215$, $R^2 = 0.9866$ *Coated tablet; N/A- Not applicable

Note: Acceptable limit of deviation for this uniformity of weight test is less than $\pm 5\%$ of the mean percentage deviation. Acceptable limit for disintegration time for uncoated tablets is less than 15 minutes while for coated tablets is less than 60 minutes (BP, 2017). The acceptable limit of hardness of a tablet is 4-10 kg/cm².

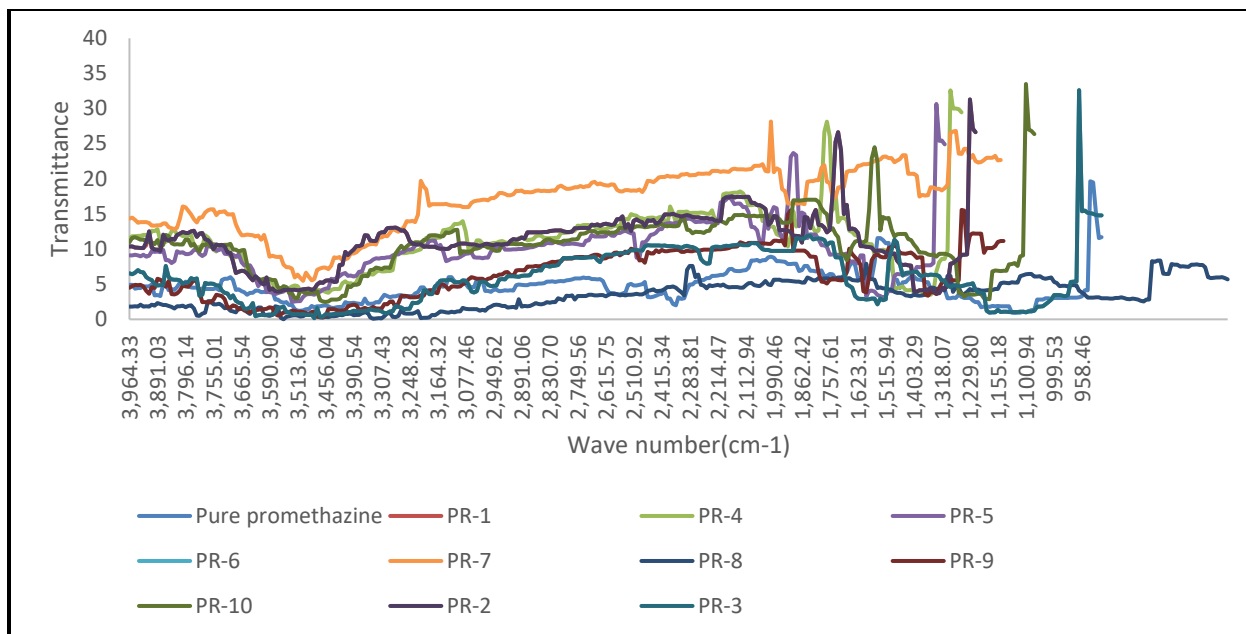


Figure 2: Overlaid FTIR spectra of Pure Promethazine as against brands of promethazine tablet samples

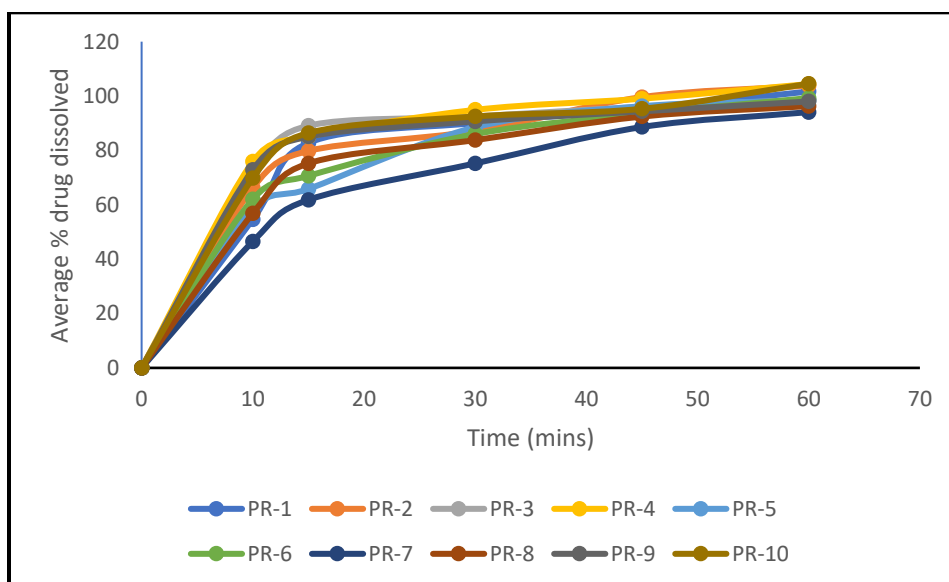


Figure 3: Dissolution rate profile of brands of promethazine hydrochloride tablet

Table 3: T50%, T75%, T90% and f_2 values of different brands of promethazine tablets.

Sample code	T50%	T75%	T90%	Similarity Factor
PR-1	<15 min	< 15 min	< 30 min	
PR-2	<15 min	<45 min	<45 min	56.38247
PR-3	<15 min	<45 min	<45 min	95.51122
PR-4	<15 min	<45 min	<45 min	61.58981
PR-5	<15 min	<45 min	<45 min	93.09224
PR-6	<15 min	<45 min	<45 min	85.22494
PR-7	<15 min	<45 min	<60 min	40.45541
PR-8	<15 min	<45 min	<60 min	72.66773
PR-9	<15 min	<45 min	<60 min	95.51122
PR-10	<15 min	<45 min	<60 min	99.92774

The BP specification is that uncoated tablets should disintegrate within 15 min and coated in 60 min. Brand PR-7 and PR-8 were coated tablet and had disintegration time beyond 60 mins thereby not complying with specifications. The disintegration time details are as stated in Table 2.

Assay results. The procedure was carried out protected from light, due to the photolabile property of promethazine. The results showing the content of active pharmaceutical ingredient using UV spectrophotometric method are shown in Table 2. Samples of PR-1, PR-2 PR-3, PR-4, PR-7 and PR-8 with percentage content of 97.10 ± 0.04 - 103.05 ± 0.05 % complied with the British Pharmacopoeia set limit for promethazine hydrochloride tablet which states that such tablets should contain not less than 95.0 % or more than 105.0 % of the label claim [17]. Percentage content obtained for samples of PR-5 (94.19 ± 1.02 %) and PR-6 (61.32 ± 2.04 %) were not up to the specified range, this is not unexpected as they also failed weight variation test and could result in sub-therapeutic effect when ingested. PR-9 (128.54 ± 0.39 %) and PR-10 (183.19 ± 0.11 %) were overly higher than the BP specified range. This may be that the degradation products of these samples are demonstrating absorbance at the same wavelength of absorption as promethazine drug itself thereby causing a very high absorbance reading which consequently resulted in increased the percentage content.

Dissolution test. Dissolution test is an important quality parameter as it monitors the impact of manufacturing process and environmental storage conditions upon the rate of drug release from a tablet.

There was a sharp release of the active pharmaceutical ingredient within 10 min after which release was sustained although gradual. All the batches except PR-7 released more than 80 % of their drug content within 30 min but

PR-7 also had 75% of its content released in 30min. Brand PN-10 exhibited a slightly greater release than other samples. The USP [19] and BP [18] specifies that the amount of drug released should not be less than 80% of the labelled amount at 30 min. All the brands but PR-7 complied as shown in Figure 3 and the release profile are almost superimposable. Thus, all the batches passed the dissolution test and their active pharmaceutical ingredient would be readily bioavailable for absorption when ingested.

Analysis of similarity factor. Two dissolution profiles are considered similar and bioequivalent, if f_2 is between 50 and 100 [20]. A T90% of 30 minutes is satisfactory and is an excellent goal [23]. In this study, parameters like T50%, T75%, T90% and f_2 were derived from the dissolution profiles of the different brands. From table 3 which showed the f_2 values of different brands in respect of brand PR-1, f_2 values for all brands except PR-7 were more than 50. Thus, they are similar with brand PR-1 and can be used interchangeably. For brand PR-7, f_2 value was less than 50 and hence may not elicit adequate therapeutic effect due to its poor dissolution profile. Therefore, it is not similar with brand PR-1 and cannot be used interchangeably.

Conclusion. The identification tests carried out for the batches of the tablet show the presence of promethazine hydrochloride except for PR-7 and PR-8 and this could be suggestive of chemical inequivalence. Also, the assessment of mechanical strength and disintegration profile were found to be in accordance with compendial specifications, however PR-9 and PR-10 failed the friability testing. The content of active ingredient for PR-1-4 did not differ from label claim and these were found to comply with the BP standards. PR-5 and PR-6 had a shortfall from the specified limit while PR-9 and PR-10 gave significantly higher values for content. The dissolution profile showed all studied brands

except PR-7 releasing up to 80 % of their active pharmaceutical ingredient within 30 min which complied with the BP and USP set limit. Of all ten brands of promethazine tablets evaluated, PR-1-4 could be considered pharmaceutical equivalents, PR-5-10 could not be adjudged to be equivalents seeing that they did not all fulfil critical quality parameters.

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